LEARNING WITH SMARTPHONES

Case study of learning drug prescribing using the PharmaFrog app

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PRELIMINARY REMARKS

I would like acknowledge the indispensable contributions of the following individuals and institutions:

1) This thesis' advisors
2) Programmers
3) PharmaFrog app concept and content developers
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5) My family and friends for moral support and encouragement.

The PharmaFrog app can be downloaded using the following QR codes.

Android

iOS

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ABBREVIATIONS

Abbreviation	Explanation
↑	Increase activity
↓	Decrease activity
ADRs	Adverse Drug Reactions
API	Application Programming Interface
CM	Clinical Mechanism
CM-G	Clinical Mechanism Group
D	Drug
eML	Electronic Mobile Learning
IT	Information Technology
IUPHAR	International Union of Basic and Clinical Pharmacology
KE	Knowledge Element
LT	Learning Theory
LU	Learning Unit
MOOC	Massive Open Online Course
MM	Molecular Mechanism
MM-G	Molecular Mechanism Group
WHO	World Health Organization

SUMMARY

Background: Smartphone-based electronic mobile learning (eML) has a potential to transform and improve teaching worldwide and particularly so in resource-limited settings. To fully realize this potential, there is a need for a validated eML framework.

Goals: To build, implement and test an eML framework applicable to a complex body of knowledge using drug prescribing as a study case.

Execution: Functionalities of leading learning apps were analyzed for relationships with learning theories (LTs). A consensus selection of functionalities related to adaptive, interactive and personalized learning were implemented and tested for learning outcome in the drug prescribing app PharmaFrog.

Outcomes: The resulting learning framework of PharmaFrog has at its core learning activities derived from Cognitivism, followed by Behaviorism and Constructivism. They provide the learner with an interactive, personalized and adaptive learning experience. The specific, implemented elements include chunking, personalization, interactivity, reinforcement, repetitions, case scenarios, adaptive learning, summary, associations, linking concepts, cues, discrimination, feedback and sequenced learning. Altogether, they form the basis of the four learning modes of PharmaFrog. App usage data provided a preliminary, but robust evidence for a learning effect.

ZUSAMMENFASSUNG

Hintergrund: Smartphone-basiertes elektronisches mobiles Lernen (eML) hat das Potenzial, den Unterricht weltweit und insbesondere in ressourcenbeschränkten Umgebungen zu verändern und zu verbessern. Um dieses Potenzial voll auszuschöpfen, ist ein validiertes eML-Konzept erforderlich.

Die Ziele: Aufbau, Implementierung und Erprobung eines eML-Konzepts, welches auf komplexes Fach anwendbar ist, am Fallbeispiel der Verschreibung von Medikamenten.

Durchführung: Die Funktionalitäten führender Lernanwendungen wurden mit Lerntheorien (LTs) in Beziehung gesetzt. Eine konsensfähige Auswahl von Funktionalitäten, die mit adaptivem, interaktivem und personalisiertem Lernen zusammenhängen, wurde implementiert und hinsichtlich des Lernergebnisses in der Arzneimittel Verschreibungs-App PharmaFrog getestet.

Ergebnisse: Das resultierende Lernkonzept von PharmaFrog besteht im Kern aus Lernaktivitäten, die vom Kognitivismus abgeleitet sind, ergänzt durch den Behaviorismus und Konstruktivismus. Sie bieten dem Lernenden eine interaktive, personalisierte und adaptive Lernerfahrung. Zu den spezifischen, implementierten Elementen gehören Portionierung der Inhalte, Personalisierung, Interaktivität, Verstärkung, Wiederholungen, Fallszenarien, adaptives Lernen, Zusammenfassung, Assoziationen, Verknüpfung von Konzepten, Hinweise, Diskriminierung, Feedback und sequenziertes Lernen. Insgesamt bilden sie die Grundlage der vier Lernmodi von PharmaFrog. Die Daten zur Nutzung der App lieferten einen vorläufigen, aber robusten Nachweis für einen Lerneffekt.

INTRODUCTION

Deficiencies in drug prescribing

Drug prescribing constitutes one of the most common health care-related activities. In many settings, it is carried out not only by doctors, but also by other medical personnel, such as nurses and pharmacists (Logendra et al., 2012). Drug prescribing is a complex and multidisciplinary process crucially depending on the skill of the prescriber. This skill is a composite of the absorbed knowledge and the individual, subjective experience. Deficits in these two variables, especially in the quality and up-to-datedness of the absorbed knowledge result in suboptimal treatments at the expense of patients and healthcare systems.

The global health-economic costs resulting from preventable medication errors are unknown, but undoubtedly enormous, based on the $21 billion annually estimated for the United States alone (AfHRa, 2010; Stan, 2018). In 2012 (Rottenkolber et al., 2012), it was estimated that patients in Germany incur an extra cost of €970 and have 2.9 days longer stays in hospitals because of adverse drug events.

Reasons for poor prescribing among fresh medical graduates in resource-limited settings

Prescribing quality is inadequate particularly among recent graduates of medical schools, who write an over-proportional share of prescriptions (Dean et al., 2002). Thus, 10% of prescriptions written by fresh medical graduates in the United Kingdom contain errors (Dornan et al., 2009; Ryan et al., 2014), most commonly wrong drug or dosage, inconsideration of allergies and of contraindications, failure to adjust dosages in patients with renal or hepatic dysfunction, and deployment of inappropriate drug combinations (Agrawal, 2009).

The study by Tibyampansha (2015) indicates that prescribing deficiencies occur worldwide, with medical students from resource-limited settings being additionally less aware of shortcomings of their drug prescribing skills. Similarly to what has been reported for developed countries (Dornan et al., 2009; Ryan et al., 2014), drug prescribing deficiencies in resource-limited settings have been attributed generally to inadequate training, and specifically to:

- the shortage of faculty for the preclinical prescribing-relevant curricular subjects, such as physiology, general pharmacology, and clinical pharmacology (Agyepong et al., 2017; Barteit et al., 2019; Mullan et al., 2011).
- limited access to high-quality and up-to-date resources such as textbooks (Barteit et al., 2019). To some extent this is also caused by the poor awareness of the existing scholarly resources. For example, WHO provides a free access to scholarly resources *'HINARI'* (Katikireddi, 2004), but very few students, teachers and librarians are aware of it, or know

how to use them, as reported from Nigeria and Tanzania (Ajuwon and Olorunsaye, 2013; Frandsen et al., 2017).

- underappreciation or simply lack of knowledge of evidence-based clinical guidelines (Barth et al., 2016), which in part reflect their length and complexity.

Educational remedies

The WHO Guide to Good Prescribing (De Vries et al., 1994) constitutes a good foundation for designing specific prescribing courses. However, it is a guideline and not a tangible tool translating directly in the practice.

The Prescribing Skills Assessment (PSA) in the United Kingdom, and the Dutch web-based prescribing learning and assessment program (P-scribe), are the most outstanding initiatives to reduce prescribing errors. The PSA is a "2-hour online assessment comprising various aspects of prescribing defined within the outcomes of undergraduate education identified by the United Kingdom General Medical Council'' and is mandatory to all final year medical students' in the United Kingdom (Maxwell et al., 2017). P-scribe is based on the WHO 6 Step treatment model described in the Guide to Good Prescribing (Tichelaar et al., 2020). The major limitations of these two initiatives are the limited penetrance due to the associated subscription costs. Additionally, PSA focuses on assessing rather than learning or teaching prescribing skills. Furthermore, there is no satisfactory smartphone solution for learning prescribing skills (Haffey et al., 2014; Le et al., 2014).

This thesis attempts to develop a complementary electronic mobile learning (eML) solution, the PharmaFrog app, which focuses on self-learning and self-assessment and is free-of-charge for all healthcare students and workers. The concept of this smartphone-based solution is presented in the following section.

The overall concept of PharmaFrog

PharmaFrog is an app which aims at improving drug prescribing quality, particularly in resource-limited settings. Indeed, PharmaFrog was inspired by, and is developed in consultation with students, including those from Kilimanjaro Christian Medical University College (KCMUCo) in Moshi, Tanzania. PharmaFrog captures with minimal redundancy and integrates all major prescribing-relevant curricular elements, i.e.:

- physiology and general and clinical pharmacology - to explain mechanisms of drug action and the principles of an efficient and safe drug deployment
- pathophysiology - to explain disease process and its therapeutic modulation using drugs
- guidelines-based therapies, including drug applications in specific and common clinical situations.

PharmaFrog presents information using physiology as a basis to create logical connections among Knowledge Elements (KEs) adapted in their length to the smartphone format. In this logic (Figure 1), disease represents a departure from a normal physiological status and pharmacotherapy is an attempt to restore the normal physiology or at least to alleviate the symptoms.

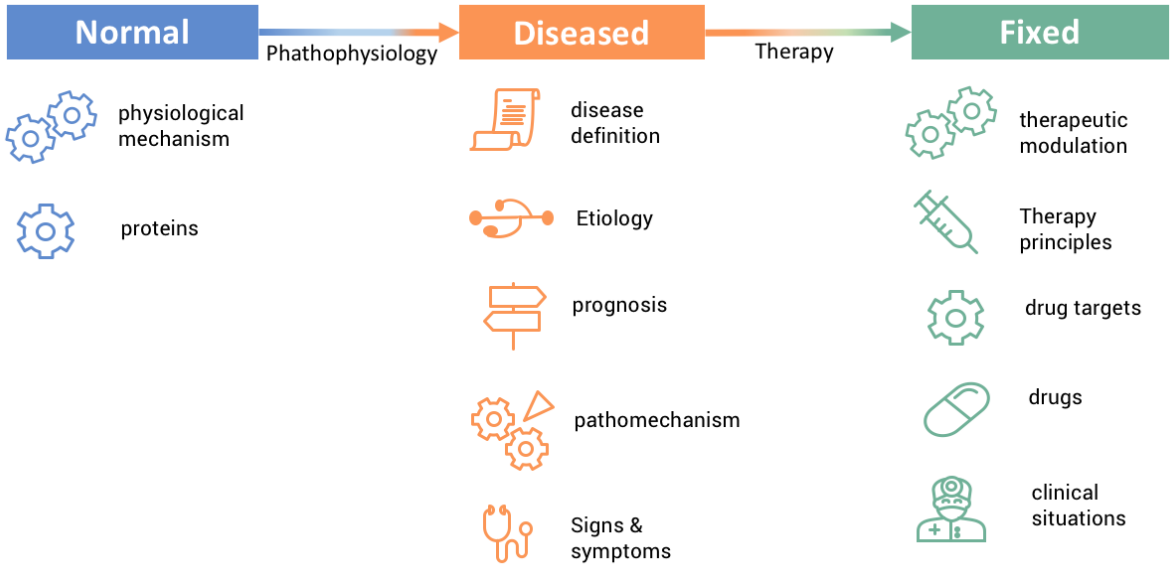

Figure 1: The overall concept and selected KEs of the PharmaFrog app.

All PharmaFrog information is stored in a relational database, the elements of which can be kaleidoscope-like rearranged and presented depending on the user's need and interest (Figure 2), for example beginning with:

- a drug and its mechanism, proceeding to clinical use (for preclinical students)
- a disease, including its pathophysiology and specific prescribing situations (for more advanced students).

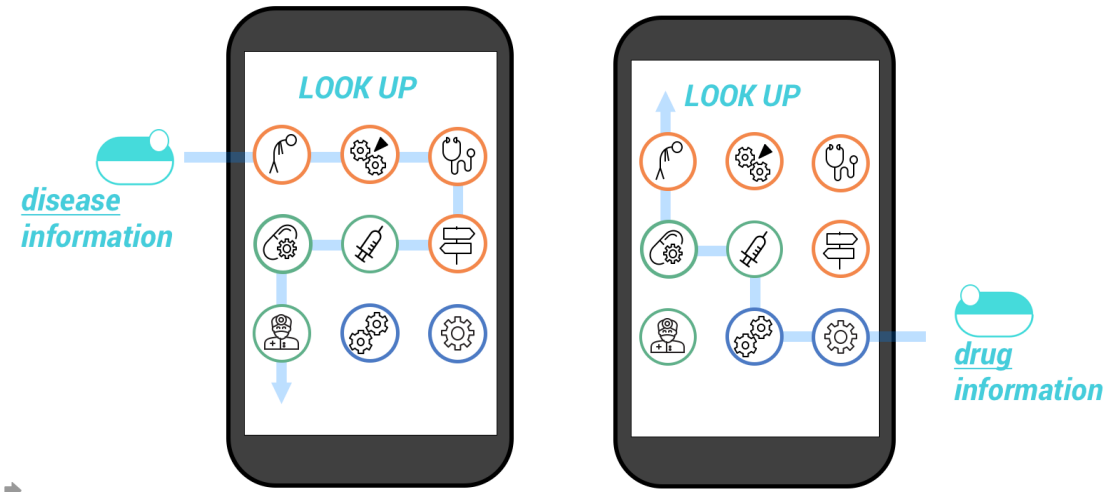

Figure 2: Schematic representation of sample PharmaFrog user journeys for information lookup.

Need for a PharmaFrog learning framework

Willis (2009) emphasizes that "any learning intervention must be based upon some theory of learning and/or cognition". As explained in detail in the Background section, learning theory (LT)-derived principles aid instructors in choosing the right learning activities for different learning and learner needs. LTs "may be considered at the level of knowledge acquisition, skill development and reflective practice" (McInerney and Green-Thompson, 2017). Therefore, it is important that PharmaFrog is built upon the foundations of LTs.

There are a multitude of LTs that serve different learning needs and purposes. This leads to the question that this thesis seeks to answer: **what learning elements and from which LTs are suitable for learning how to prescribe drugs using the PharmaFrog app?** How this question was answered is described below in the Thesis Goals and in Work Plan sections.

Thesis structure

This report is comprised of the following sections:

1) Background summarizes the status of application of LT-derived activities to eML in a broader context of learning and education.

2) Methods describe the tools and procedures used to develop the PharmaFrog learning framework, to implement it in the app, and to deploy and evaluate the app by a target audience.

3) Results present outcomes of executing the methods. It also presents the interpretation of the results and shows how they influenced the design of the learning framework.

4) Discussion provides an inference of the results, how they are related to other similar studies, and how they contribute to a wider field of research. Achievements and limitations that hindered the smooth running of the project are also outlined, followed by recommendations for further work.

THESIS GOALS

The overall goal of this thesis is to **build, implement and evaluate an eML framework applicable to a complex body of knowledge**. Drug prescribing serves as a study case. Functionalities of leading learning apps will be analyzed for relationships with LTs and for evidence of improving learning outcomes. Functionalities judged best to achieve the set learning goals will be implemented and tested in the drug prescribing app PharmaFrog. The resulting learning activities will be mapped to LTs that support them. The purpose is to establish a comprehensive, yet understandable set of learning activities to achieve learning impact with PharmaFrog taking into consideration the mobile device affordances. The specific objectives are:

1. The development of a learning framework for PharmaFrog through identification and combining learning-promoting activities from:

   1.1 selected LTs

   1.2 selected, leading, preferentially medical eML apps

   1.3 student and expert recommendations.

2. The implementation of the learning framework into the PharmaFrog app.

3. The evaluation of the app for usability and acceptance.

Simultaneously, this thesis aims at reducing the number of prescription errors. To this end, the framework resulting from this thesis will be made available permanently as an interactive module of the app enabling self-learning. The target audience are healthcare students and professionals, i.e medical doctors, nurses and pharmacists, especially those in resource limited settings, with a particular emphasis on recent graduates. The learning module will allow for acquisition, update and retention of an individually defined level of pharmacotherapy-related knowledge and skills.

WORK PLAN

Objectives	Specific tasks
1	1.1 Identify learning activities in selected LTs 1.2 Analyze selected popular eML tools for LT activities 1.3 Analyze previous PharmaFrog research for recommended learning activities 1.4 Describe the PharmaFrog learning framework
2	2.1 Implement first app prototype app with lookup functionality (version 1.0) 2.2 Deploy and evaluate app for user behavior (version 1.0)
3	3.1 Expand the app functionality to include interactive learning activities (version 2.0) 3.2 Test and Evaluate the app (version 2.0) for user acceptance and learning outcomes

BACKGROUND

Learning vs. education

PharmaFrog app is designed for self-learning how to prescribe drugs. The terms learning and education sometimes are used interchangeably; sometimes they are juxtaposed in opposition, as in the famous aphorism commonly attributed to Albert Einstein "The only thing that interferes with my learning is my education". Therefore, it is important to first define and differentiate between the two (Table 1).

	Learning	**Education**
Definition	the acquisition of knowledge or skills through study, experience, or by being taught	process of receiving or giving systematic instruction, especially at a formal setting
Knowledge source	acquired from various sources	typically, from a teacher and/or from defined and structured materials
Guidance	require neither an educator nor guidance	typically, under the guidance of an educator
Motivation	prompted by intrinsic motivation	prompted by extrinsic motivation
Process	not a systematic process	systematic process
Age	not limited by age	typically received up to a certain age

Table 1: Differences between education and learning (Pediaa, 2015, modified).

Learning, as defined by educational psychologists, is "a process that brings together cognitive, emotional and environmental influences and experiences for acquiring new or modifying one's existing knowledge, skills, behavior, values, and views" (Rhalmi, 2011). It follows that learning is a lifelong process: humans learn from birth on until death, i.e. as long as they interact with other people and with the environment. Most learning occurs in the absence of any formal setting or guidance and it is driven by intrinsic motivation rather than by compulsion.

Against this background, **education** could be considered simply the part of learning that is compulsory in the first two decades of life. A closer look suggests that education is much more a set of organizational measures meant to facilitate or even enforce learning. These measures include settings such as school buildings and personnel, curricula, and teaching schedules. In the best case, education allows for a degree of individuality regarding learning interests and schedule. Invariably, it is used to promote worldviews shaped by the local political system. In consequence (and the worst case), education is sometimes misused to promote the survival of autocratic regimes, warmongering, irrational worldviews, and racial hatred. Artistically, this sinister side of education (not of learning!) was addressed memorably by the 1979 song *"We don't need no education"* by Pink Floyd, Another Brick in the Wall album.

Importantly, technological developments increasingly blur the distinction between education and learning. Thus, Keegan (2005) categorizes education into conventional and distance education. **Conventional education** takes place in schools, training centers and workshops. It involves interactions between the teacher and the students, as well as among the students themselves. Conventional education is alternatively referred to as traditional education, face-to-face education, and instructor-led-training. Taken together, it is defined by the rightmost column of Table 1.

Distance education takes place away from the study center and, in most cases, it is mediated by technology, most prominently by the Internet. Students have a choice of when, where and how to study. In consequence they have less, or even none at all, physical contacts with the faculty and peers. In the absence of a detailed study plan, or of compulsory presence, they require strong motivation and may tend to use more extracurricular sources. Taken together, distance education is best defined by various combinations of characteristics from the middle and rightmost columns of Table 1, i.e. by education and learning.[1]

The ultimate impact of technology on teaching and learning cannot be foreseen. It could be argued that in a world where all relevant information is stored in the cloud and accessible everywhere, in most cases free of charge, teaching should focus on information retrieval. In consequence, the importance, or at least the volume of formal education would diminish. In fact, imposters (Murray et al., 2011; Romania Insider, 2019) have been remarkably successful in many complex and regulated educational programs, including medicine. This demonstrates that, in principle, any educational framework could be substituted by self-directed learning. However, this may work only for particularly and unusually motivated individuals. In the foreseeable future, educational frameworks will continue to control the access to all but most basic professions. Nevertheless, the contribution of self-learning will grow, not the least due to the development of mobile technologies, which are discussed in the following.

eML

By the mid-1990s, electronic mobile technologies initiated an enormous transformation in communication, management, commerce, entertainment, and – crucially – education (Sharples, 2000). This development accelerated further a decade ago with the introduction of smartphones, tablets, and of broad-band Internet. The number of smartphones has already exceeded that of this planet's inhabitants (Boren, 2014) and app stores brim over with learning apps written by stakeholders ranging from enthusiastic amateurs to educational corporations. This has ushered in the most dramatic change in teaching and learning since the beginning of formal schooling. Many higher education institutions are implementing eML to complement the existing electronic learning (e-learning) systems and to provide more flexibility in learning (Yeap et al., 2016). The most obvious manifestation of these developments is the ongoing shift from physical classrooms to increasingly virtual and individual learning environments (Bettinger et al., 2017).

[1] For the record, distance education/learning is much older than computers and the Internet. For the Western world, it started with the invention of mass printing in Mainz in the 15th century, which ushered in an unprecedented and thus far unparalleled improvement in literacy and knowledge (Lau et al., 2017).

eML differs from other types of e-learning by its **mobility**, enabled by portability and wireless connectivity, which allow for instant **information access** (Ally, 2005; Mehdipour and Zerehkafi, 2013; Yeap et al., 2016). eML is thus categorized as a subtype of distance education (Keegan, 2005). Sharples et al. (2005) distinguish eML from other types of learning based on **learner's mobility**, as learners are mobile and learning takes place outside the formal learning environment. In contrast, Traxler (2005) focuses on the mobility aspect of the **device** and defines eML as "any educational provision where the sole or dominant technologies are handheld devices such as smartphones and tablets".

The effects of eML on learning outcomes, frequently considered obvious, in fact remain poorly characterized. Admittedly, eML enables learning according to the needs and opportunities (time and location) and deploy novel learner-motivating rewards, such as those offered by individual or group-based gamification (Bettinger et al., 2017; Herbert et al., 2014; Prieto et al., 2014). On the other hand, eML suffers from limited attention span due to distractions (e.g. incoming messages), from the absence of direct (physical presence-based) supervision and of classroom/peer-driven motivation, or simply from eye strain resulting from the small screen size (Bettinger et al., 2017; Kuznekoff and Titsworth, 2013).

Crucially, there is no convincing evidence that the introduction of eML in the 1990s, particularly of smartphones in 2007, has improved the dissemination and quality of knowledge. Just the opposite is possible, since the largely unregulated ecosystem of the Internet has made it more difficult to distinguish reliable sources of information from scientific fake news. Therefore, this work assumes that applying eML is currently justified for areas insufficiently covered by the existing and validated resources, especially printed ones. A typical example of such areas is drug prescribing, this thesis' case study. This is due to:

- insufficient access by the learners
- rapid knowledge evolution
- complexity, e.g. driven by interdisciplinarity.

LTs

LTs are conceptual frameworks that describe how learning takes place i.e. how learners acquire, process and retain knowledge (Driscoll and Van Barneveld, 2015; MacCallum and Parsons, 2016). LTs may be used to analyze or modify an existing, or to create a completely new, learning environment. Specifically, LTs should be considered in teaching in order to make informed decisions on (Anderson, 2004; Goel, 2017):

- design, development and delivery of knowledge by providing a basic understanding on how people learn and a way to explain, describe, analyze and predict learning effects
- different learning and learner need by offering frameworks that help understand how information is used, how knowledge is created and how learning takes place

- how to best invest time and resources effectively.

There are a multitude of LTs, most of which were developed before the introduction of electronic mobile technologies. The most prominent classical LTs are behaviorism, cognitivism, and constructivism (Driscoll and Van Barneveld, 2015; Keskin and Metcalf, 2011).[2] Briefly, **behaviorism** focuses on a learner's change in behavior triggered by conditioning and reinforcement by reward or punishment. **Cognitivism** focuses on how the brain processes information i.e. the learner's motivation, determination and capacity to process information in a meaningful and memorable way. **Constructivism** views learning as a process in which the learner actively constructs or builds new ideas or concepts based on experience (Benjamin, 2016). A LT attempt for the digital age is **Connectivism** (Siemens, 2014). This LT emphasizes the importance of the social context and that learners construct knowledge from different sets of information distributed across the web. Learners need to connect to the internet to share or find new information (Kop, 2011). There is currently no single LT that is considered to be superior and to guarantee perfect results. Rather, educational curricula and activity frameworks are structured based on a combination of elements from various LTs, depending on the needs and circumstances (MacCallum and Parsons, 2016).

Considering how profoundly theory underpins learning activities, it is imperative that eML interventions are driven by LTs. eML activities have more impact if they are mapped to the appropriate LTs (MacCallum and Parsons, 2016). The following section discusses the status of LTs application to eML.

The lack of a validated LT for eML

Until now, no specific, formal LT has been proposed for eML. Instead, several researchers have:

- developed a checklist for testing a theory of mobile learning
- developed eML-specific frameworks based on conventional LTs
- analyzed the classical LTs in the context of eML.

Checklists

Sharples et al. (2005) outlined a checklist that should be used to differentiate any eML theory from other LTs. The checklist comprises of the following five questions:

- *"Is it significantly different from current theories of classroom, workplace or lifelong learning?*
- *Does it account for the mobility of learners?*
- *Does it cover both formal and informal learning?*

[2] Brief characteristics of all nine LTs considered in this thesis are provided in Appendix A.

- *Does it theorize learning as a constructive and social process?*
- *Does it analyze learning as a personal and situated activity mediated by technology?"*

Frameworks

Frameworks are not LTs but rather ways to evaluate and frame mobile learning solutions (MacCallum and Parsons, 2016). They can be adopted for conceptual understanding of a mobile learning solution and for designing eML applications (Koole et al., 2018). Frameworks for eML include but are not limited to:

- the framework for Rational Analysis of Mobile Education (FRAME) by Koole (2009), which provides technical, social and individual aspects to consider while deploying eML. These aspects and the interfaces between and among them encompass the key characteristics and functionalities of eML as shown in Table 2 Kearney et al. (2012) associated these aspects with socio-cultural LT.

Aspect	**Characteristics**
device usability	● input and output capabilities ● storage capabilities. ● hardware and software capacity
learner	● prior knowledge ● memory capacity of learner ● context and transfer ● discovery learning ● emotions and motivations
social aspect	● conversation and cooperation ● social interaction
device usability and learner intersection	● ease of use ● portability ● information availability ● psychological comfort ● satisfaction
device usability and social aspect intersection	● connectivity e.g. internet, Wi-Fi, GPRS, Bluetooth ● collaboration tools
learner and social aspect interaction	● interaction ● situated cognition ● learning communities

Table 2: eML characteristics as defined by Koole et al. (2009).

- the framework by Kearney et al. (2012), which extends the FRAME by focusing more on pedagogy aspects. They identified three features of eML pedagogy, i.e. authenticity,

collaboration and personalization, resulting from the socio-cultural LT. Personalization focuses on tailoring learning activities to give learners a sense of ownership. Learners have control of the learning environment, pace, time and can set their own goals. Authenticity focuses on providing tasks that are applicable to real-life situations, they could be simulated or real. Collaboration focuses on creating a mediation for social interactions. As a result of applying this framework on two eML projects, the researchers recommend it for use to assess eML pedagogical impacts and designs.

- the 3-Level Evaluation Framework (3-LEF) by (Vavoula and Sharples, 2009), which provides a structured format to assess usability, educational and organizational impact and their inter-relationships. 3-LEF operates on the following three levels:
    - Micro level, which examines the individual activities of users and assesses the usability and utility of a given educational technology system
    - Meso level, which examines the learning experience as a whole, to identify learning breakthroughs and breakdowns
    - Macro level, which examines the impact of a new technology on established educational and learning practices and institutions.
- the framework of ubiquitous knowledge construction by (Peng et al., 2009). The framework puts 'mobile learners are the center of knowledge construction'. The framework outlines hierarchical components, beginning with eML-supporting tools and learners, through pedagogical methods, to achieving ubiquitous knowledge construction. The fist hierarchy takes into consideration mobile learners and utilization of ubiquitous computing. The second hierarchy applies constructivism and life-long LTs. The third hierarchy is the learning vision.

The existing learning frameworks have mostly been used for evaluation eML designs as reported by Koole et al. (2018) in their evaluation of the FRAME and 3-LEF application. They also noted the use of these frameworks across a wide range of topics and fields of study, most prominently in the field of language learning and in the higher education setting.

Classical LTs in eML context

Some researchers have already attempted to identify LTs that are most applicable to eML. Using the connection between LTs and electronic mobile device affordances defined by Parsons et al. (2016), MacCallum et al. (2016) identified six LTs that are the most suitable for eML: behaviorism, constructivism, experiential learning, situated cognition, community of practice and connectivism. They provide two contrasting eML app examples, a language learning app and a physical woodland exploration app. They noted that the language learning app utilized learning principles derived from behaviorism, constructivism, connectivism and communities of practice LTs. These results were to some extent similar to the earlier research by Leńko-Szymańska and Boulton (2015), who also identified constructivism, cognitivism and social-cultural LTs as common LTs applied in eML solutions for languages. The physical woodland exploration app utilized learning principles of

connectivism, experiential learning, constructivism, communities of practice and situated cognition. Unfortunately, the researchers only provided few exemplary eML activities for each LT and not detailed lists.

Taken together:

- there is no LT for eML
- most attempts to analyze classical LTs in eML context, or to develop eML frameworks, have focused on language adaptations. There are neither LTs nor frameworks for eML solutions in the field of medicine, which is in focus of this thesis and is described in the following.

The potential of eML in medical education

With the rapid growth of medical knowledge, it is challenging for busy physicians and medical educators to stay updated with all the knowledge necessary to provide quality health education and care (Guze, 2015). The number of new articles indexed by MEDLINE at the National Library of Medicine was 904,636 for the year 2018 alone (MEDLINE, 2019).

In resource limited countries, medical education is additionally challenged by drastic increases in student enrollments. This is the result of a political drive to meet the World Health Organization (WHO) recommendation of a minimum number of one physician per 1000 population (Kumar and Pal, 2018). However, the number and capacity of the medical schools is insufficient. These schools do not have enough teaching resources such as staff, internet connectivity, and up-to-date teaching content. To address these limitations, some schools have attempted to integrate technology into their teaching by providing internet connectivity and dispensing tablets to medical students to facilitate learning outside of the classroom. For example, in Ethiopia, students were given tablets with preloaded textbooks. In Tanzania and Botswana, students and teachers were provided tablets in order to access the learning management systems and other resources on the internet (Kelly et al., 2019; Lisasi et al., 2014; Vovides et al., 2014).

eML carries an enormous potential to improve medical education and thereby delivery of health care education and care. This is based on the following trends and observations:

- The proliferation of mobile devices technology that provides instant worldwide access to almost any source of information needed (Krull and Duart, 2017).
- The growing importance of the -rapidly changing - treatment guidelines based on the evidence-based medicine.
- Changes in learning and information retrieval behavior among students and health care workers in favor of digital mobile solutions. There is increasingly more worldwide acceptance of eML among medical students and healthcare professionals (Quant et al., 2016). These “digital natives” (Prensky, 2001) are accustomed to technology and expect their learning environments to embrace it (Guze, 2015). A survey by French (Frensch,

2019) on 478 students from Germany and Tanzania revealed that 88% of them had smartphones. Among smartphone owners, 60% had 1-5 medical apps installed. Every fifth respondent used medical apps for more than 30 minutes daily.

METHODS

Identification of learning elements

From LTs

Peer-reviewed literature, commercially published media, and grey literature were searched for scientific evaluations of LT elements and how they are applied to eML. A literature search was done on Google scholar using keywords such as “learning theory”, “mobile learning theory”, or “mobile learning frameworks”, “mobile learning” and “learning elements”. This resulted in a list of LTs and their underpinning learning elements.

From existing mobile apps

eML solutions for medical education were also analyzed for the LT elements. The search was expanded onto other learning topics utilizing eML, fore mostly language-learning apps and Massive Open Online Courses (MOOCs). The apps selection criteria was based on app reviews such as medical app review sites such as iMedicalApps and highest ranking and trending learning apps within the Google Play Store and Apple App store. The following search terms included: “prescribing”, “learning”, “medical”, “language”, “MOOCs”, “assessment”, “continuous medical education”, “pharmacology”. The resulting elements were mapped to relating LTs

From previous PharmaFrog-related research

User feedback was obtained through a meta-analysis of the previous research related to the PharmaFrog app concept (Frensch, 2019; Tibyampansha, 2015; Westervelt, 2015). A series of the surveys and interviews on medical students in German, Tanzania and the United States were administered in these studies. The aim was to identify learning elements/functionalities preferred by health professional students for PharmaFrog.

PharmaFrog learning framework

The resulting learning elements from the three steps above were aggregated. Through several group discussions with pharmacology experts, learning elements that best fit the PharmaFrog learning goals were identified. These were used to define the learning framework.

The learning framework was then implemented into mockups for a functionality test. Microsoft PowerPoint was used to design the screen and InVision for linking the screens. InVision (2020) is a prototyping tool created for designers, by designers. InVision is a prototyping tool that allows

quick creation of interactive mockups and enables sharing them with team members or clients via a link. The mockups were evaluated by pharmacology experts and students in multiple consultation rounds.

Framework implementation

The learning framework was implemented in the PharmaFrog app using the following Information Technology (IT) structure, hosting and programming solutions:

Microsoft Azure: the servers and databases of PharmaFrog are hosted on Microsoft Azure, a commercial cloud computing platform (Copeland et al., 2015).

MySQL and SQLite: MySQL database ("MySQL," 2020) is for production. This production database stores all the PharmaFrog data. All production tasks such as creating, updating and deleting data are run on the production database. SQLite database ("SQLite," 2020) is used to store published data. This database is downloaded to the PharmaFrog app, enabling the offline use of the app.

Application Programming Interface (API): An API is a set of programming code that defines the terms of and enables data exchange between one software product and another. PharmaFrog uses a REST API (REST API, 2020). REST API uses HTTP requests to GET, PUT, POST and DELETE data. Swagger (OpenAPI) framework (Swagger, 2019) is used for automatic generation of the connector code and documentation, the latter one using plain English. The API forms URL-encoded headers for sending JSON data.

JSON: JSON is a programming language-independent data exchange format that allows easy transfer of data between applications (JSON, 2020). All descriptions, e.g. about Drugs and Indications, are structured in JSON format and then saved in MySQL and SQLite.

React Native: React Native (2020) is a JavaScript based cross-platform framework for developing native apps for Android and iOS. It enables faster development by using single code for both iOS and Android platforms. React Native has been used, among others, to create Facebook, Instagram, and Skype apps.

React: React is a JavaScript library for developing web user interfaces (React, 2020). With React, applications can either be rendered on the server, which transfers the created HTML files to the client's browser, or the application can be rendered directly in the browser or in the calling environment. React was used for designing the Admin website. The Admin website is used by editors and administrators to create and manage the PharmaFrog content.

Redux: Redux is a state management tool and can be used in JavaScript enabled frameworks (Redux, 2020). Redux uses a master state object to which app components send their requests for

state changes, and then in turn updates the states of the associated components. Examples of states in the PharmaFrog app include whether a user is signed in, a notification is opened, a question is answered, refresher is attempted, among many others.

Agile: Agile is an iterative software development methodology. Agile facilitates quick development of software products by utilizing iterative processes and constant user feedback (Agile Alliance, 2015). The development proceeds in small chunks (sprints), with each sprint building upon the lessons and feedback from the previous sprint (Figure 3).

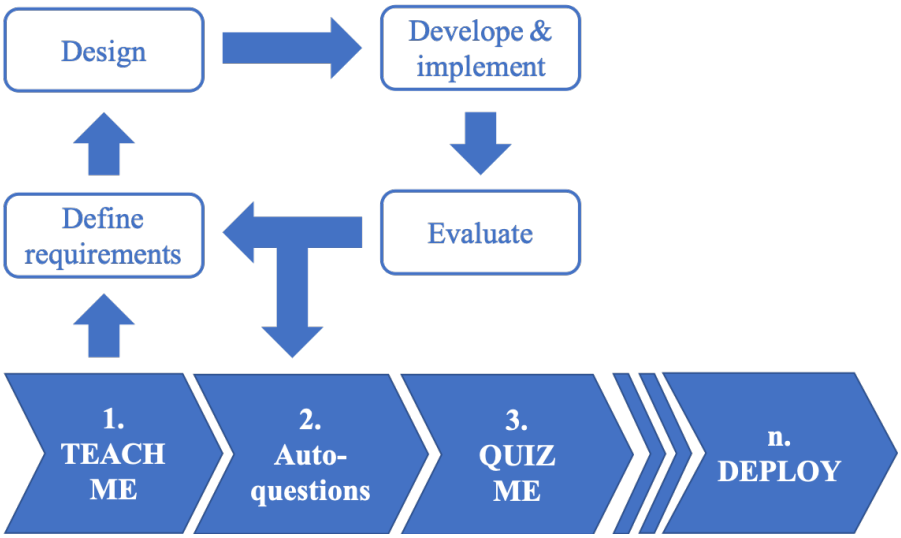

Figure 3: Examples of sprints of PharmaFrog development and the typical processes underlying each individual sprint.

User outreach and feedback collection

App users outreach

Potential PharmaFrog users were reached via emails collected during previous PharmaFrog activities and via contacts to several faculties of medicine and pharmacy in Tanzania. Emails of student associations and professional groups and teachers of pharmacology from all over the world were collected from their respective websites.

Social media, specifically WhatsApp groups, Facebook and Twitter were used to reach out to medical student association groups and pharmacology discussion groups.

Surveys and interviews

Interviews and survey questionnaires were used to collect user feedback and to assess user perceptions of the app. The collected information was used to capture who the PharmaFrog users

were and what was their assessment of the user friendliness, structure, and content scope of the app. This information was used to develop recommendations for changes and corrections.

The survey questions were compiled together with pharmacology experts. The survey was deployed electronically via the PharmaFrog app. This was to ensure that the survey is attempted by only individuals who had actual interaction with the app. Several face to face group discussions and interviews guided by the survey questions were carried out in four medical schools and two schools of pharmacy in Tanzania. The app store ratings and reviews were also collected.

App usage analytics

User interactions with PharmaFrog were collected using Google Analytics for PharmaFrog version 1.0 and, beginning with the publication of PharmaFrog 2.0, by Matomo installed on the server of the University Medical Center Mainz, Germany. All user activities were recorded anonymously. Among others, the collected data was used to determine:

- the general app usage, including the preferred functionalities such as SHOW ME, TEACH ME, or QUIZ ME, the preferred navigation paths ("user journeys"), the most visited articles, and drop-off points.
- the time spent interacting with the app, the number of sessions over a given period of time and the intervals between visits. A visit is a group of user interactions beginning with opening the app until stopping interacting for at least 30 minutes.
- the learning behavior and learning effects using e.g. the question response history.

Data analysis

Data sorting and transformation was conducted using Python 3.7.3. Descriptive statistics were performed using GraphPad Prism 8.4.0.

Two Sample proportion Z-test was performed in Python with the statsmodels 0.11.1 library.

The Sankey diagrams were generated using sankeyMATIC website accessible via http://sankeymatic.com/build/

RESULTS

Elements for PharmaFrog learning framework

As there was no validated LT for eML, an eML framework was built using suitable **learning elements**[3] identified:

1) in classical LTs
2) in leading educational apps
3) in previous surveys of the PharmaFrog concept
4) through testing of learning elements identified in 1), 2) and 3) using mockups of the PharmaFrog app.

From LTs

MacCallum et al. (2016) and Leńko-Szymańska and Boulton (2015) identified a total of 7 LTs applicable to eML. However, neither of these important contributions provided a comprehensive list of specific learning elements underpinning the LTs. Therefore, the LTs dealt with by these authors[4] and expanded by situated learning, social cognitive theory and social constructivism, were analyzed for learning elements.

The results for all nine LTs assessed are given in detail in Appendix A and in a summary form in Table 3. The identified learning elements were grouped into 17 arbitrarily chosen, higher-order **learning activities**. Many learning activities were shared by multiple LTs (marked blue in Table 3). Collaboration was the most shared activity, appearing in eight LTs, followed by case scenarios and coaching, each of them appearing in five LTs. Most activities were found in one or more of the following three LTs: behaviorism, cognitivism, and constructivism.

[3] Learning elements are 'parts of an education simulation design that are deliberately crafted and incorporated in a way to support the learning experience' (Reiners et al., 2015).
[4] The connectivity LT was excluded because it highly depends on social media, which was not contained in the intended scope of PharmaFrog.

Learning activity	Description	Exemplary learning elements	Learning theories								
			Behaviorism	Cognitivism	Constructivism	Situated learning	Experiential learning	Communities of practice	Sociocultural	Social cognitive theory	Social constructivism
Associations	applying explanations to facilitate understanding	metaphor, explanations	■	■							
Case scenarios	build relation with the real-world context with real-life situations	real-life situations, apprenticeship, role playing		■	■	■	■			■	
Chunking	grouping information into small units to reduce information load	topic divided in small units		■							
Coaching	an expert supports a learner by providing training and guidance.	direct instruction, scaffolding	■		■	■			■		■
Collaboration	social opportunities	discussions, group activities	■	■	■	■	■	■	■		■
Critical thinking	analysis of facts to form a judgement	reflection, exploration, brainstorming			■	■	■		■		
Cues	a word or small piece of information that helps to guess an answer or relate to a concept more easily	outlining, mnemonics, hints	■	■							
Discrimination	get incorrect choices far from the correct choice	matched non-examples, analogies	■	■							
Feedback	corrective feedback	negative or positive feedback	■	■							
Illustrations	visual presentation of a concept or process	images, diagrams	■	■	■					■	
Interactivity	active engagement of a learner	questions, generative learning	■	■	■						

Linking concepts	associate new content with something known	concept mapping, links to prior knowledge									
Reinforcement	consequences applied to strengthen learning	penalties, rewards, rules									
Repetition	learning a concept over and over again in order to make it clear or master it	Leitner system, flash cards									
Sequencing	organizing learning content in efficient and meaningful ways	organize topics logically									
Schedule	planned activities with time and order to be done	timetables used mostly in MOOCS									
Summaries	restatement of main points	summaries									

Table 3: Learning activities and elements from LTs. LTs a given activity has been identified in are marked blue.

From existing eML apps

Forty-three apps for languages, medical education, and MOOCs were analyzed between March and May 2017 for the deployed learning elements. The apps were selected via Google Play Store and Apple App store using the following inclusion criteria:

- trending status
- rating of three and more on a scale of five
- recommendation by review sites (for medical apps)
- free-of-charge availability.

The 43 selected apps included 12 language apps, 25 medical apps, 2 mathematics apps, two MOOC platforms and 2 general, MOOC-like apps with no preset course sequence (Appendix B).

The learning elements identified in the apps were mapped to the activities defined in Table 3. The result is shown in Table 4. The analysis revealed four activities not noted among LT-related activities listed in Table 3. They included personalization, linking text to external sources, learning levels, and placement tests (Table 4).

Activity	Learning elements	Deployed in apps (%)				
		language n=12	medical n=25	mathematics n=2	general n=2	MOOCs n=2
Associations	additional information & explanations	0	20	50	50	100
Case scenarios	case scenarios	8	48	0	0	0
Coaching	live tutor	8	4	0	0	0
Collaboration	team activity	33	32	0	50	100
Cues	hint of what will be covered in a lesson / highlight key words	42	8	0	0	50
Feedback	feedback from users	0	12	50	50	50
Illustrations	illustrations	75	52	0	100	100
Interactivity	games	8	0	50	0	0
	questions	42	44	50	0	100
	flash cards	8	20	0	0	0
Learning levels	beginner, intermediate, advanced	17	4	0	50	50
External links	link to external sources e.g. guidelines	0	36	100	0	100
Personalization	search	8	16	0	100	100
	save information	8	56	50	100	100
	study modes	0	4	0	0	0
	customization	25	24	50	50	0
Placement test	placement test	33	0	0	0	0
Reinforcement	assessment	0	0	0	0	50
Reinforcement	status of progress	50	36	50	50	100
	rewards	50	28	50	50	100
	penalty	8	4	0	0	0
	reminders	25	12	0	0	100

Repetition	requiring the learner to read the information over and over again	42	8	0	50	100
Schedule	timed (duration to take the course)	8	8	0	0	100
Sequenced learning	order of learning topics matters	33	0	0	0	100
Summary	review of test/quiz/assessment	33	24	50	0	50

Table 4: Learning activities identified in 43 learning apps. The colors indicate the frequency of occurrences of an activity in apps, with green depicting the most and red no occurrences at all. Activities additional to those listed in Table 3 are highlighted.

As depicted with blue bars in Figure 4, the most prevalent learning activities across all apps were personalization (63%) illustrations (60%), reinforcement (58%), and interactivity (56%). The least used activities were cues (2%, found exclusively in medical apps), coaching (4%, found in medical and language apps), recommendations (6%), and placement tests (8%, found exclusively in language apps).

More detailed attention was then paid to language and medical apps, because they accounted for a majority of the apps analyzed. In language apps (orange line in Figure 4), the most frequent activities were illustrations (75%), reinforcements (58%), and interactive learning (50%). In medical apps (green line in Figure 4), the most used activities were personalization (72%), reinforcement (56%), interactivity (56%), and illustrations (52%).

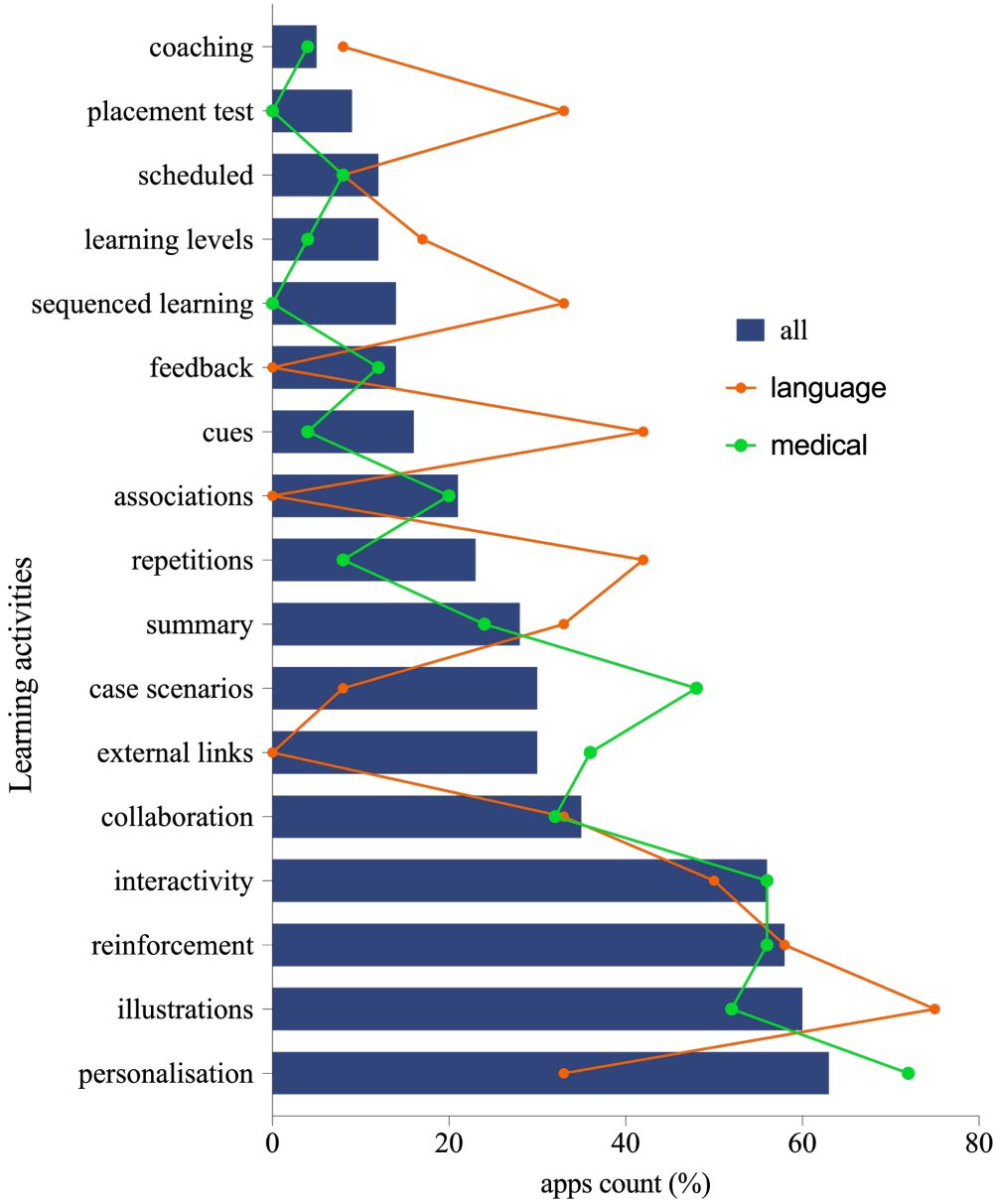

Figure 4: Learning activities from apps.

From preceding PharmaFrog mockups and surveys

A meta-analysis was performed on all the previous research done about the PharmaFrog app concept in fulfilment of Master's degrees (Frensch, 2019; Tibyampansha, 2015; Westervelt, 2015). These studies deployed, among others, surveys and interviews of medical students in Germany, Tanzania and the United States. The aim was to identify learning elements/functionalities preferred by health professionals and students, the main target users of PharmaFrog.

Frensch (2019) developed the first concept of the reference functionality termed as SHOW ME. He tested the concept using a simulation and a survey on 478 students from Germany (69%) and Tanzania (31%). His simulation covered the following features and activities:

- offline access
- app content consisting of Indications, Drugs, Mechanisms, Contraindications, and Adverse Drug Reactions (ADRs)
- interactive learning (learning modules followed with multiple choice questions)
- quizzes
- app content search

The simulation evaluation got a very positive reception. The content scope was considered sufficient by over 85% of the respondents for each content section. Ninety-three per-cent of survey respondents indicated interest in using the app for learning purposes.

Westervelt (2015) expanded on Frensch's concept and simulation to include communication. She explored in the same cohort how PharmaFrog users could benefit from collaboration. Her simulation covered the following communication activities:

- notes, both kept private and public
- information sharing through emails
- content-based discussion forum
- saving and sharing favorite content
- search for geographically close users, enabling connecting with each other.

Most African students (66%) showed interest in using the app for communication, in contrast to German students (3%). Both cohorts showed interest in private notes and in saving favorite content.

Tibyampansha (2015) evaluated the use of PharmaFrog for decision support. This involved a prescribing simulation tool covering one disease (arterial hypertension) case scenario. The case scenario was designed to follow the WHO prescribing steps (De Vries et al., 1994). Thus, it focused on the identification of pre-existing condition(s), specifying diagnosis based on present symptoms, selecting the relevant treatment objectives, selecting the most suitable drug from the hospital drug list, specifying the initial dosage, preparing the patient for possible ADRs, explaining consequences of not taking the drug, recommending additional, non-pharmacologic measures, and setting the time-point for the follow-up visit. The last one included checking if the therapeutic objectives have been reached, assessing any ADRs, and hypothetical treatment adjustments in case of ADRs as well as in cases of none or insufficient response to the initial treatment.

The simulation was tried on 10 students from Tanzania. All 10 participants stated that they would use such a tool for their clinical work. The diagnosis and drug selection aids were considered particularly useful.

The resulting PharmaFrog learning activities

All the learning elements resulting from the analyzes of LTs and of mobile apps, and from preceding mockups and surveys, were aggregated and evaluated for inclusion into the PharmaFrog app. The evaluation was conducted together with pharmacology experts and content developers, including students. The learning elements selected for inclusion are presented in Table 5. For simplicity, their LT relatedness is restricted to behaviorism, cognitivism, and constructivism.

Learning activity	**PharmaFrog learning elements**	**Behaviourism**	**Cognitivism**	**Constructivism**
Chunking	Presentation of information in small chunks termed KEs		■	
Personalization	Choice of learning modes (SHOW ME, TEACH ME, QUIZ ME, REFRESHERS)			
	Choice of learning pace			
	Choice of learning scope			
	Search			
Interactivity	Automatically generated questions		■	
Reinforcement	Proficiency gain from answering questions and from reading content via TEACH ME	■		
Repetitions	Proficiency decline modelled on a “forgetting curve” requiring the learner to revisit the learning content in any preferred learning mode and time	■	■	
Case scenarios	At least one indication-related real-life case scenario written by experts and presented as a question		■	■

Adaptive learning	Proficiency-based selection of: ● questions for REFRESHERS and QUIZ ME learning modes drugs and indications for TEACH ME mode			
Summary	● after Drug LUs: presentation of a summary of drug mechanisms just learned and of a list of diseases treated by the drug ● after Indication LU: presentation of a list of drugs that treat the indication just covered			
Associations	Use of icons to associate words with knowledge categories			
	Further information is provided for every question answer choice and in QUIZ ME and REFRESHERs some questions have further information at a question level.			
Linking concepts	Linking concepts using lists and in-text hyperlinks			
Cues/hints	Introduction messages for every KE in TEACH ME mode			
Discrimination	Incorrect answer choices for questions are not closely related to the correct answer choice			
Feedback	feedback links are embedded to article description cards that and every question			
	Notifications about content changes			
	General app evaluation online survey link and app store rating are embedded in the app and the user is attempted to take them after a couple of clicks			
	Automatic corrective feedback upon answering questions			
Sequenced learning	KEs presentation in TEACH ME mode follow a specific logical sequence			

Table 5: Learning activities selected for inclusion into PharmaFrog. LTs these learning activities are associated with are marked blue.

The elements in Table 5 were then implemented in mockups to simulate the desired app functionalities. The screens were designed using Microsoft PowerPoint and uploaded to InVision (https://invis.io/JBO294Y4EYT#/278149575_Index) to mimic interactivity. Figure 5 shows some of the screens from the TEACH ME, QUIZ ME and REFRESHER mockups. Numerous group discussions with pharmacology experts and medical students from Mainz were carried out to finetune the app design. The resulting learning framework concept set the stage for the programming and implementation of the PharmaFrog app.

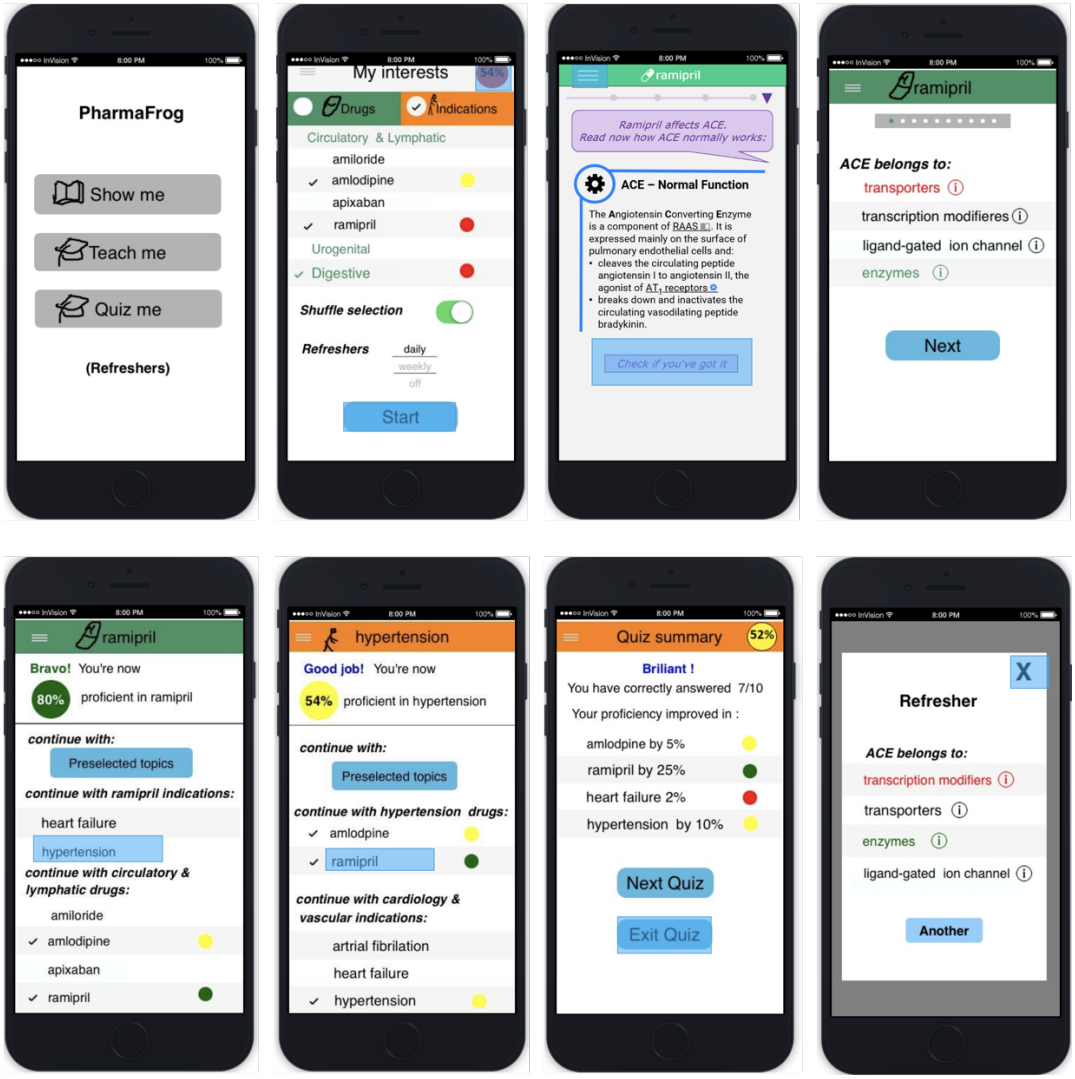

Figure 5: Sample screenshots from InVision mockups used to test PharmaFrog architecture.

PharmaFrog IT structure and hosting

Overview

Operating system-specific app installers (APK for android and IPA for iOS) are generated and distributed, respectively, via Google Play (APK) and App Store (IPA) for installation on mobile phones. The admin instance, API instance and the databases are hosted on Microsoft Azure, a commercial cloud-computing platform. Two types of databases are used: MySQL for production and SQLite for publication. The production database is updated by editors using the admin instance. Content that is ready for publication is saved to a SQLite database and made available for app download. Following the app installation on a mobile device, the SQLite database is downloaded

upon the initial opening of the app and thereafter upon each database update. All the data flows among the admin, database, and the app are controlled by the API (see Figure 6).

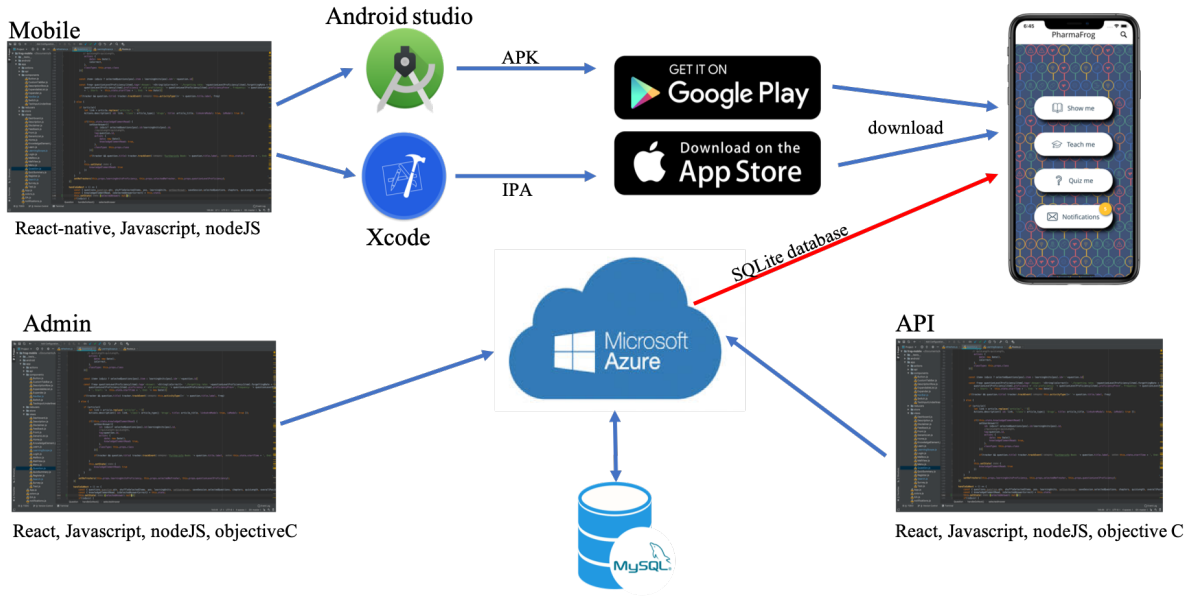

Figure 6: PharmaFrog hosting.

MySQL database

This database is used for content production. Figure 7 shows all tables and their relationships. The database content is updated by editors via the admin interface.

At the core of PharmaFrog is the **'articles'** table. An article (single row) represents the content of a single unit in PharmaFrog, for example an Indication such as hypertension, or a Drug such as ramipril, or a Mechanism such as ACE etc. The content is contained inside a JSON object.

The table **'article_categories'** records all the article major categories. These are: Drugs, Precautions and Instructions (termed "To consider" in the app), Situations, Diagrams and Summaries, Clinical Mechanisms (CMs), Molecular Mechanisms (MMs), Indications, ADRs, Physiology, Pharmacology, Case scenarios, Learning Units (LUs), Legal and Notifications. An article can belong to only one category. Articles are further classified into groups, for example (medical) Speciality, (organ) System, molecular and clinical mechanisms groups, and so on. This information is recorded in the **'article_groups'** table. An article can belong to one or more groups.

There are three audit tables:

- **"database_updates"** records the general updates of the database by the administrators such as database publications,

- **"updates"** records user interactions with the articles for evaluations of the Learn and Quiz module
- **"article_history"** records edit changes to articles.

The **“devices”** and “**sessions”** tables are used for information related to user interactions with PharmaFrog. The **“survey”** and **“feedback”** tables are used to collect user feedback about the app. The **“notification”** table records all notification messages.

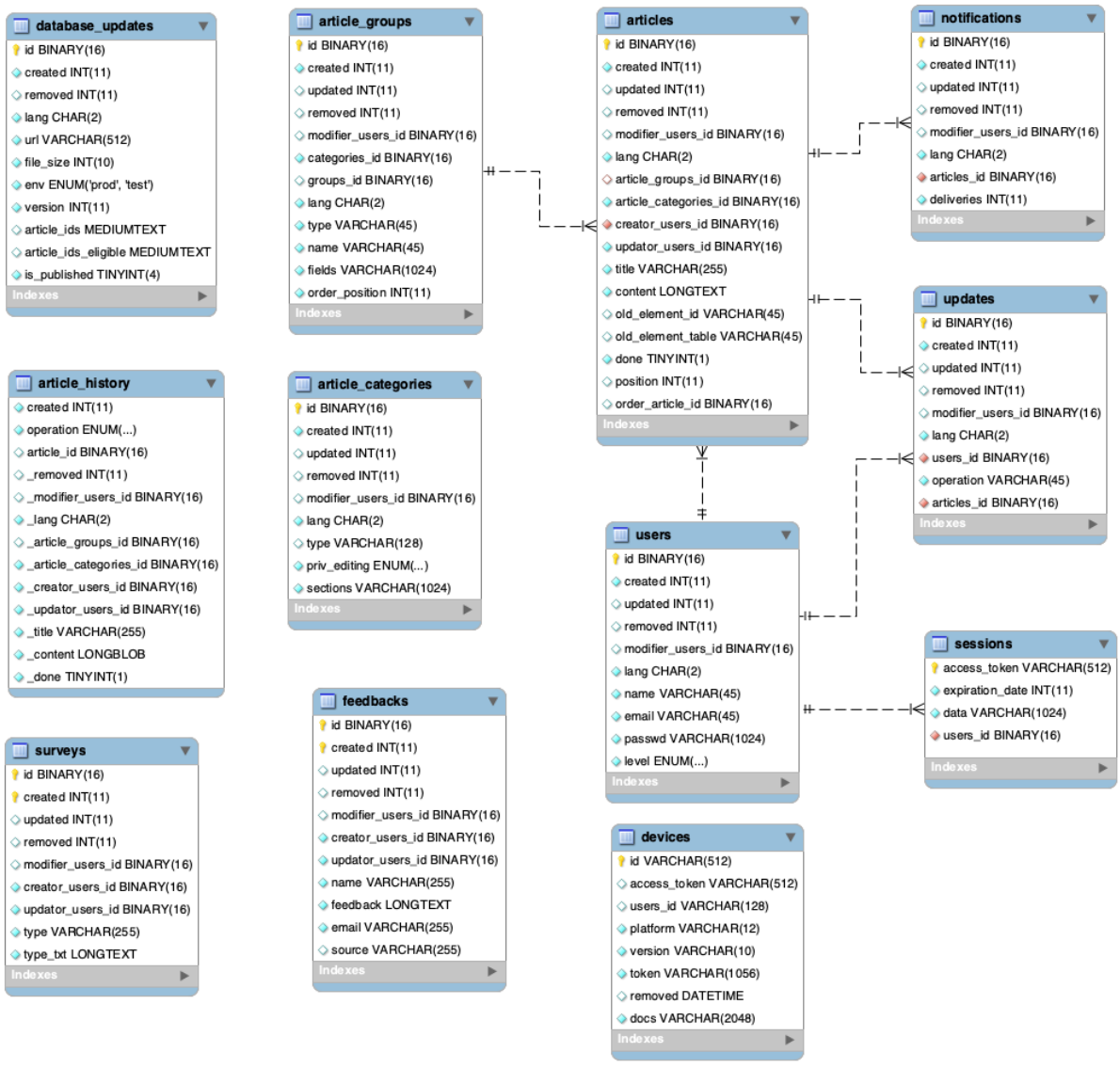

Figure 7: PharmaFrog entity relationship diagram.

SQLite database

This database enables an offline use of the app. Unlike the production database (MySQL database), it stores only the published articles. All information is aggregated in only one table termed **'articles'**. Content, including references, is contained inside a JSON object. All the data processing is done by the API, i.e. the app does not do any further computations and linking other than just displaying the information.

JSON

Because of the complex nature of the app content, the content descriptions use JSON format. For published content in the SQLite database, the JSON content is ready for rendering within the app and there is no further processing to be done. Figure 8 is an example of JSON data of the drug ramipril in the SQLite database.

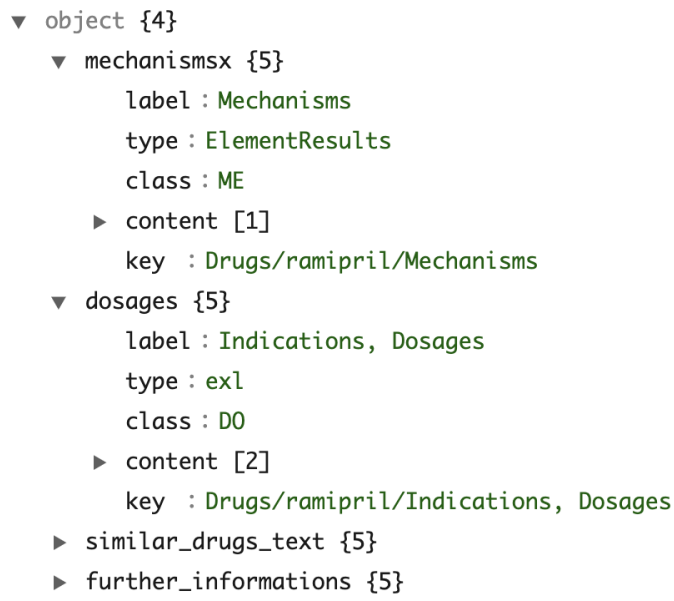

Figure 8: Sample JSON content.

Content entry and structuring

Entering content

Content is entered into the MySQL database using the admin interface. Content editors are able to create new articles, or view and edit already existing articles. The admin contains the following major content categories of data entry templates:

- Drugs, for recording a drug's:
    - clinical application, which forms the basis of the drug listing according to USED AS (e.g. as analgesics, Appendix F, image A)
    - Indications it is used against
    - dosages[5]
    - circumstances/conditions TO CONSIDER! upon prescribing (precautions, warnings, relative and absolute contraindications)[3]
    - ADRs, including their frequency and severity
    - information elements to be excluded from automatic question generation.

- Mechanisms:
    - MMs, which explain the Normal Function of a drug target and the need and drugs available for its Therapeutic Modulation.
    - CMs record information in a way analogous to MMs, but integrated on a higher level of physiology.
    - MM-Gs and CM-Gs, which record information similarly to MMs and CMs, but integrated on still higher levels of physiology.

- Conditions:[6]
    - Indication pages record the medical specialty involved, the organ system(s) affected, a brief and easily understandable summary (in a nutshell), the formal definition, etiology, prognosis, pathomechanisms, signs & symptoms, and therapy goals. For each therapy goal that involves drug therapy, the pertinent drugs and the targeted MMs and CMs are listed.[7] The card is also used to record elements not to be used for automatic question generation.
    - ADR cards have a structure similar to Indications. They are not used in the current version of the app.

[5] This information is entered separately for each combination of an indication and application route.
[6] Conditions is a supra category used for Indications and ADRs due to similarities in content structure.
[7] Why MMs and CMs cannot be simply taken over from Drug-MM-CM relationships defined in MM and CM cards is discussed in challenges.

- Clinical Situations describe frequently encountered indication-specific questions encountered in clinical practice. The situations have a Q&A form and are derived from current clinical guidelines.
- Library:
    - Physiology cards describe pertinent concepts subcategorized into cellular, organo-systemic and pathophysiology.
    - Pharmacology cards describe pertinent concepts subcategorized into drugs, general, prescribing, and tools.
- Learning
    - Case scenarios, one per Indication, are used to generate the starting questions of Indication LUs (Question A1 in Appendix D).
    - the category still under development, provisionally termed LUs, for the generation of non-automated questions.

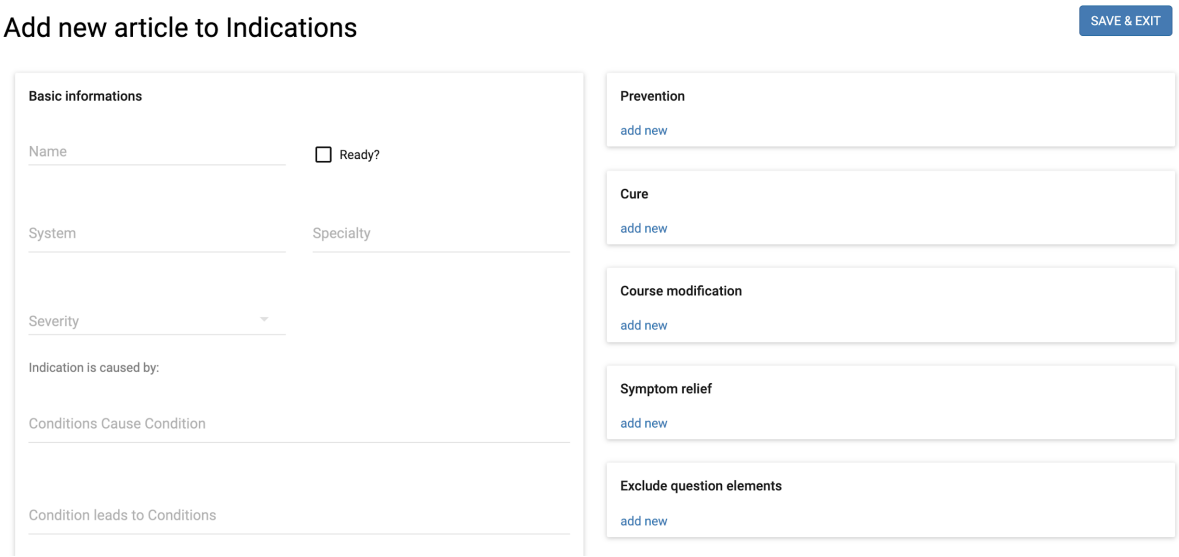

Figure 9: Example of Indication editing page.

Linking content

Most of the content linking is carried out while entering data into the appropriate admin page. For example, each drug needs to be linked to an appropriate indication, application route and so on.

In addition, KEs or app cards can be hyperlinked to from text passages they are cited in. The cards and KEs are made available for hyperlinking by typing an **"@"** sign followed by the name of this card or KE. This lists the appropriate card or KE, enabling its selection for hyperlinking. Figure 10 shows all elements retrieved for hyperlinking using the prompt @heart. This prompt is sufficient

and specific to retrieve the card for the indication heart failure and all individual KEs associated with this card.

Figure 10: Heart failure referencing sections.

Revising content

New or revised articles are made available for internal revision through checking the checkbox "ready" (Figure 9). Following login, editors and admins can view these articles in the app, through downloading the latest, as yet unpublished database (Figure 11 A). This procedure enables internal content evaluation and revision in the app format before making it public through publishing.

Publishing content

All articles are saved in the production database. Articles set to "ready" can be published in a new SQLite database. The interface for publishing (Figure 12) is accessible via Admin → Publish → Review. Besides new articles set to "ready", it lists all previously published articles that underwent changes since the last database publication. Checking the 'Published" checkbox and saving the page generates a new SQLite database ready for download to the app and usage.

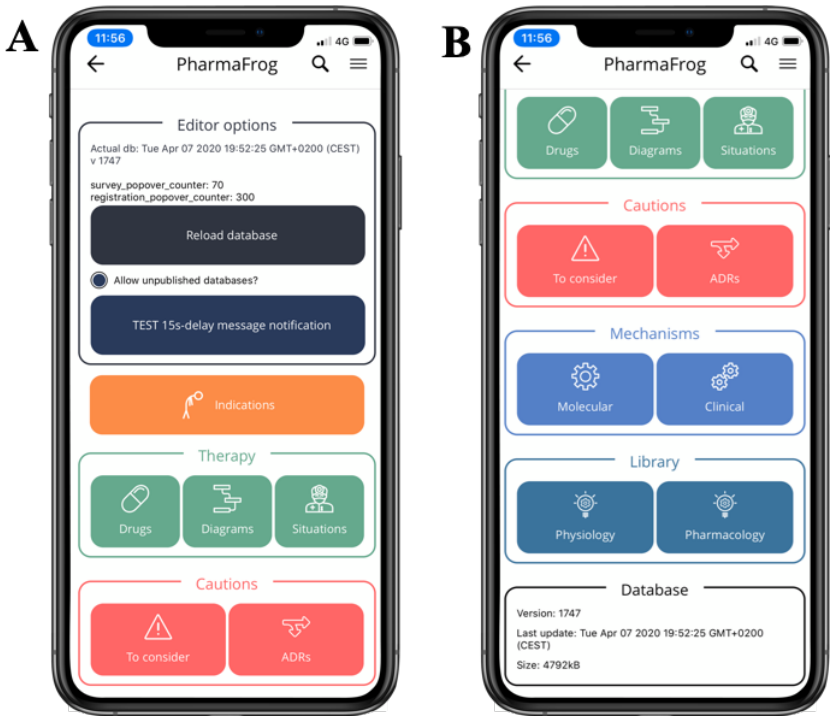

Figure 11: App version information.

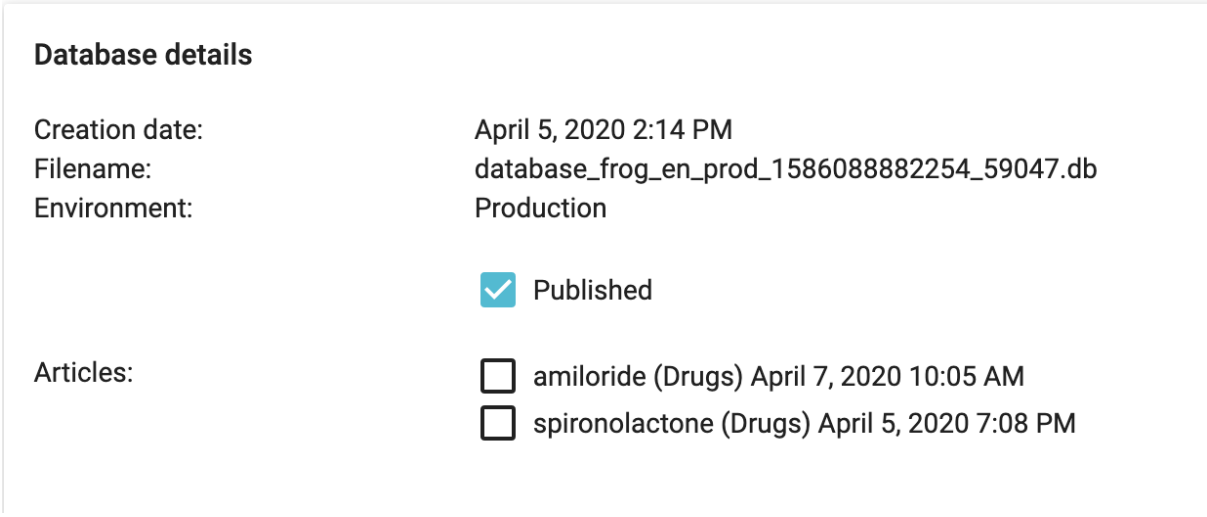

Figure 12: Interface for managing databases.

Upon opening, PharmaFrog downloads the new SQLite database via Akamai Content Delivery Network (Akamai CDN in Figure 13). The Akamai CDN is a network of servers that are optimized for content delivery through distribution among many physical locations and network nodes. It can thus react directly to user requests and provide the requested database quickly and securely. All the information flow is controlled by the API. Figure 13 illustrates the entire process of information

flow, from data entry to publication. A checklist for database publication is provided in Appendix G (I).

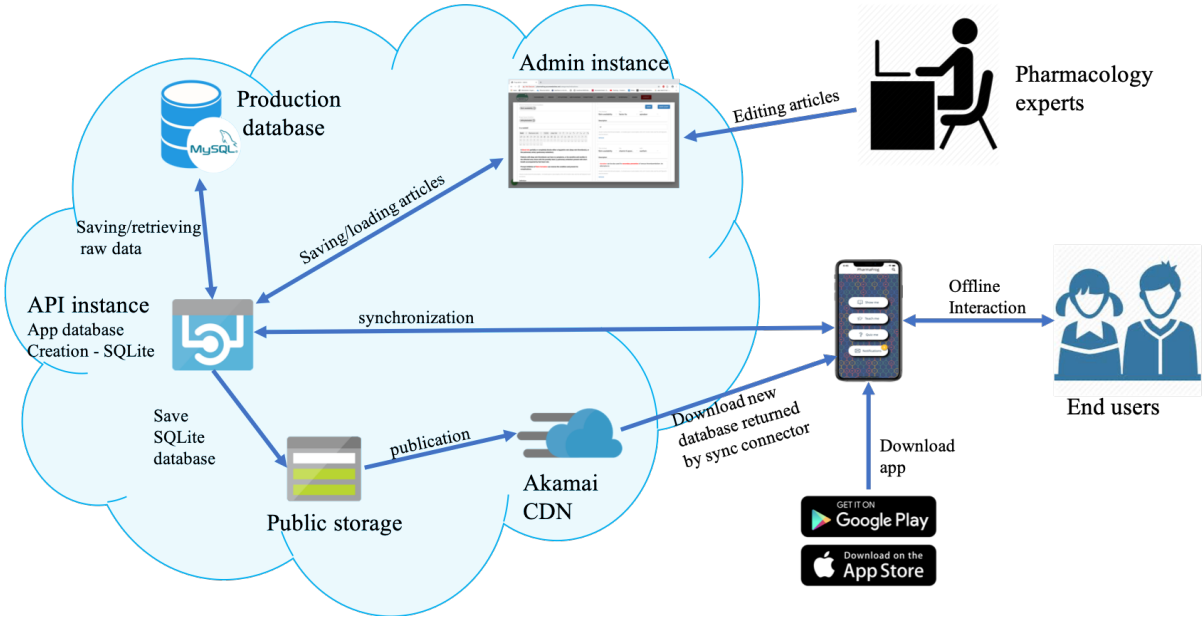

Figure 13: Information flow.

Implementation of the PharmaFrog Learning Framework

Upon commencement of this thesis in February 2017, PharmaFrog was available as:

- a general concept of a pharmacology and drug prescribing **reference app** tested in several international settings using interactive mockups and surveys
- an unpublished version developed in cooperation with an IT company located in Mainz.

The said company had ceased its operations at the end of 2016. This necessitated a complete overhaul of the app hosting and database structure. The app had to be reprogrammed from Ionic to React Native framework, a cross-platform JavaScript-based programming language which generates complete app structures for the two currently dominating operating systems, Android and iOS (Novick, 2017). This was accompanied by significant changes and refinements of data presentation and navigation throughout the app. This resulted in the SHOW ME (i.e. lookup or reference) mode, deployed as PharmaFrog 1.0 in November 2017. In December 2019, PharmaFrog 1.0 was replaced by PharmaFrog 2.0, which included modes allowing for interactive, personalized, and adaptive learning. In the following, these developments are described in more detail.

PharmaFrog 1.0

SHOW ME learning mode

General concept

PharmaFrog attempts to explain pharmacotherapies and drug prescribing on the basis of physiology. Consistent with this concept, the information in the "SHOW ME" part of the PharmaFrog (Figure 14 D) is arranged, when considered bottom-up:

- from the blue "Why it works" topics on general pharmacology and physiology of drug targets (Figure 14 F, G)
- through the red "To consider" (Figure 14 E) and "ADRs" drug prescribing safety information
- through the green "How to fix it" drug deployment information (Figure 14 A, B)
- to the orange "What is wrong" description of the indications to be treated (Figure 14 C).

PharmaFrog information is presented in small chunks. The basic unit of information is termed Knowledge Element (KE). KE is a text passage tagged with an individual icon, as exemplified by the Physiology card "voltage-gated ion channels" (Figure 14 F) and by the "Normal function" of the drug target plasminogen (Figure 14 G). All but Physiology, Pharmacology, and Clinical Situations cards are higher-order combinations (Figure 14 A), or graphical representations (Figure 14 B) of multiple KEs. Thereby, these cards emphasize causation and interrelatedness[8] and - in case of Indication cards - also chronology.[9]

Examples of card and list concepts

All cards of PharmaFrog were created based on multiple discussion rounds with students and pharmacology experts. All cards contain innovations, or represent entirely new concepts. Innovative are also the various list (Appendix F) used throughout the app. Several illustrative examples are presented in the following.

- **MMs** (Figure 14 G) and **CMs** (termed as 'Clinical' in Figure 14 D) cards each consist of a Normal Function and a Therapy Modulation KE. The separate presentation of the normal function and modulation of a drug target/CM allows for an incremental introduction of

[8] Causation and interrelatedness are emphasized also by Wikipedia-like in-text hyperlinks, e.g. "cell membrane potential" in Figure 10 F, which link KEs to KEs contained in other cards.
[9] From etiology through pathophysiology, signs and symptoms to therapy.

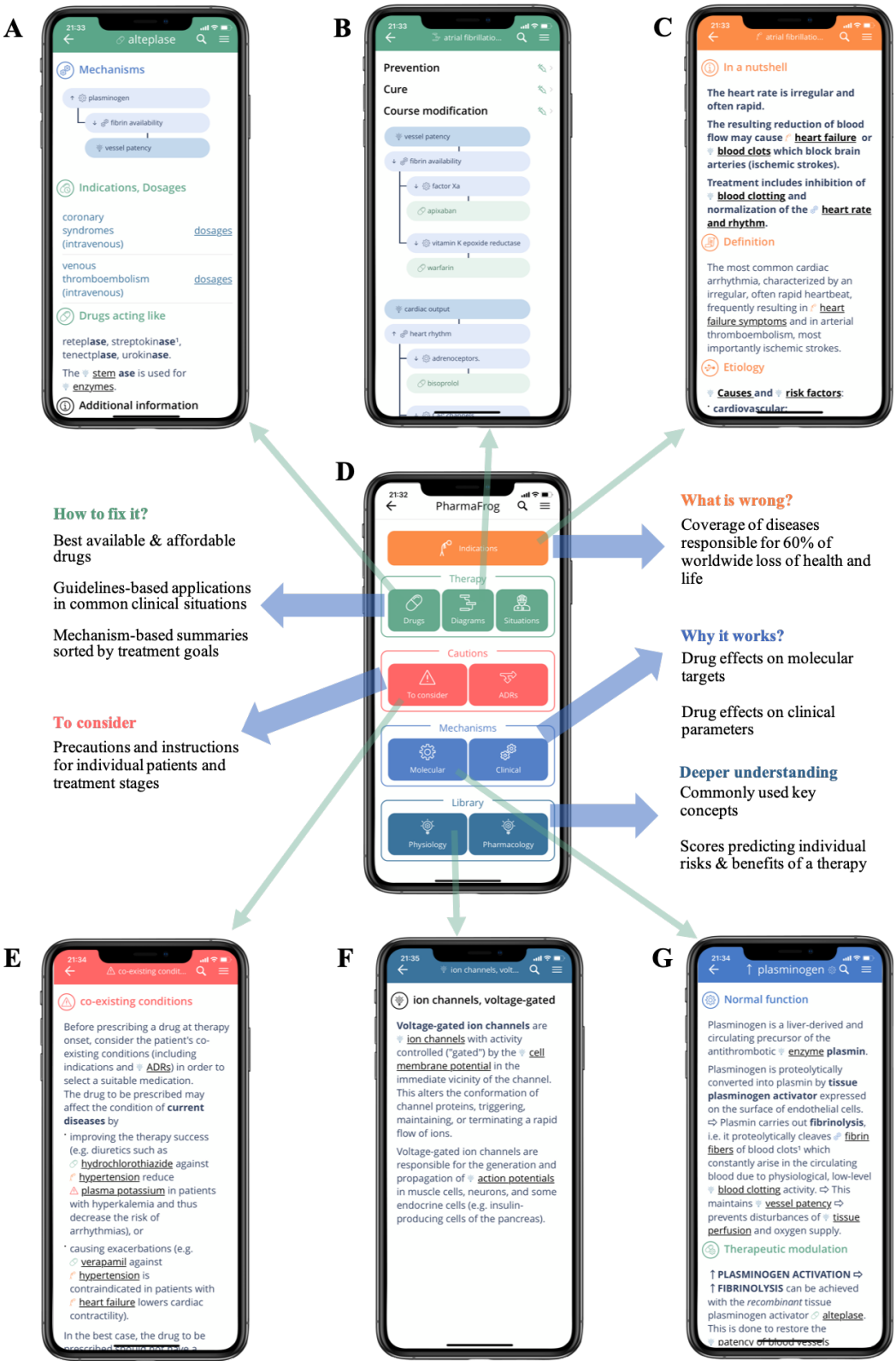

Figure 14: The SHOW ME mode of PharmaFrog.

these KEs in LUs, and for a maximally stringent relationship between a KE and questions derived thereout.

- **Clinical Situations** ('Situations' in Figure 14 D) are Q&As based on the latest treatment guidelines. Treatment guidelines are notoriously long, complex, and thereby difficult to implement. Clinical Situations convert treatment guidelines into the most common situations a health care worker may encounter. Clinical Situations are arranged in a chronological manner.

- **To consider** cards (Figure 15 A and B) likely constitute the most innovative and potentially extremely useful category, especially in its WHEN listing. This category integrates some 20 patient- and drug-related parameters that need to be considered while contemplating, carrying out, monitoring, and terminating drug treatments. This information is usually dispersed as warnings, precautions, relative and absolute contraindications, and dosage adjustments within the drug approval materials such as Summaries of Product Characteristics issued by the European Medicines Agency. PharmaFrog integrates this information into a medical practice-oriented **timeline** subdivided into subsections Therapy Onset, During Therapy, and Therapy End (Figure 15 A). [10]

- **Treatment Goals** clearly differentiate among prevention, cure, course modification, and symptom relief. These goals are linked to the pertinent MMs and CMs and drugs in Diagrams (Figure 14 B) and in Indication cards.

- **Indications** (Figure 14 C) compile the following KEs in a chronological order:
    - In a nutshell: a summary of the indication in plain language
    - Definition: a formal but brief description of the nature, signs and symptoms, and treatment of the indication
    - Etiology: causes of or risk factors associated with the indication
    - Prognosis: forecast of the likely outcome
    - Pathomechanisms: processes through which the indication develops
    - Signs & symptoms: objective and subjective abnormalities indicative of the given indication
    - Therapy Goals: therapy options specified according to pertinent treatment goals (prevention, cure, course modification, symptom relief).

[10] This timeline is reminiscent of checklists for the individual flight phases takeoff/climb, en route, and descent/landing.

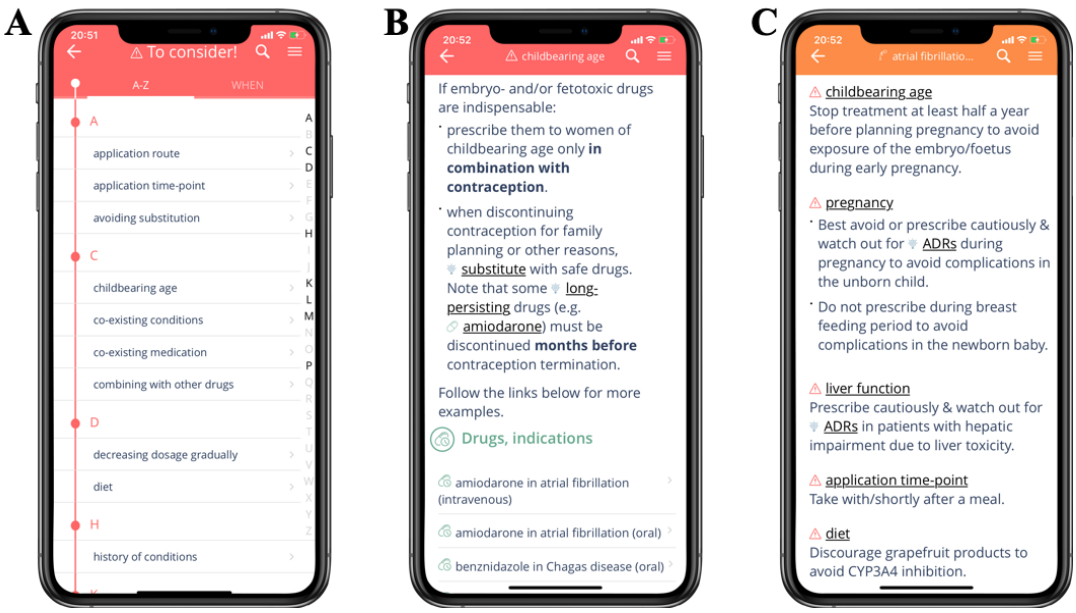

Figure 15: The beginning of the "To consider" card list grouped according to the therapy stage; (B) Partial content of the "To consider" card "Childbearing age"; (C) The specific "To consider" entry for the drug amiodarone to be prescribed and administered intravenously against atrial fibrillation to a female patient of childbearing age.

Deployment and evaluation of SHOW ME mode

The SHOW ME mode was published in Google play store and Apple app store in November 2017 as PharmaFrog 1.0. Potential app users were reached out using mailing lists and social media, mainly Facebook and Twitter. In the two medical schools in Tanzania available for visitation, the app was presented by the researcher to about 70 students in small discussion groups of about 5-15 students.

The app onboarding and use were observed for a period of 8 months (Nov 2017 – May 2018). The app had 1190 installations from 99 countries (Figure 16). The majority of the installations were from Germany (43%) and Tanzania (14%), due to intense contacts with students at three medical faculties in these countries.

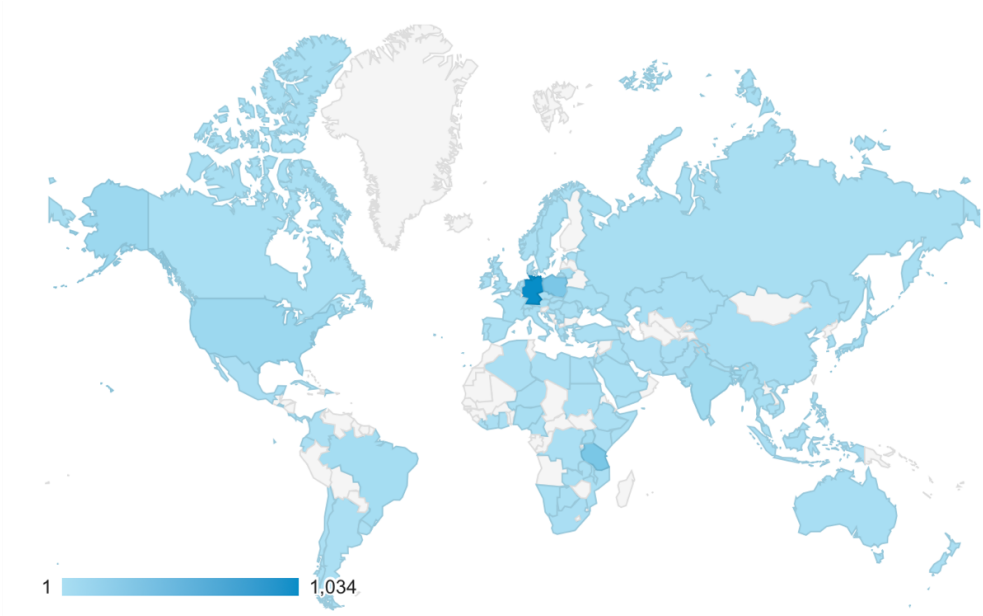

Figure 16: The worldwide distribution of the first 1034 downloads of PharmaFrog 1.0.

Altogether there were 4299 sessions with the app. A session is a group of user interactions beginning with opening the app until stopping interaction for at least 30 minutes. The dashboard screen (Figure 14 D) was the first screen displayed upon opening the app. On average, users spent 5.4 minutes per session. Figure 17 visualizes the initial paths followed by users. Most users accessed information beginning with Drugs (45%) and Indications (18%). This observation formed the basis for the decision to focus on Drugs and Indications as the main categories of the learning modes TEACH ME and QUIZ ME for PharmaFrog 2.0.

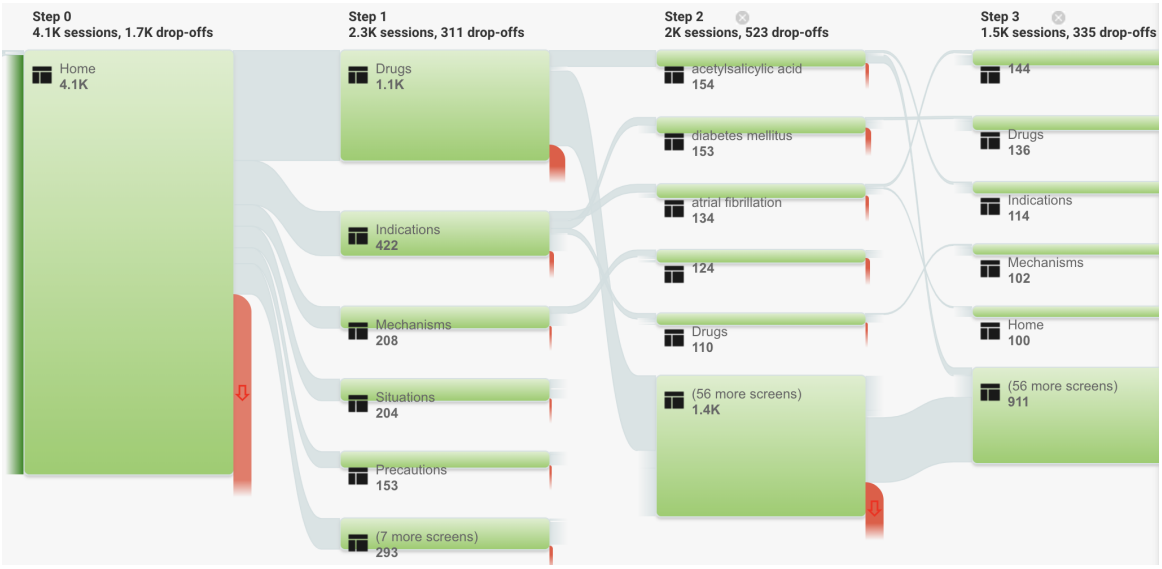

Figure 17: The first three steps of user journeys through PharmaFrog 1.0.

PharmaFrog 2.0

The launch of PharmaFrog 1.0 was immediately followed by the development and programming of functionalities going beyond SHOW ME, in particular those enabling **interactive, personalized, and adaptive learning**.

Interactivity

Interactive learning actively engages the learner with the learning content. This is achieved in PharmaFrog 2.0 through deployment of Drug- and Indication-derived questions of two types: single-answer choice (Figure 19) and, in one case (Figure 20), multiple-answer choice. Questions are generated automatically using predefined templates connecting two or more KEs. Users' answers are used to calculate an estimate of user proficiency in Drugs and Indications a given KE belongs to. Questions are deployed in the three interactive PharmaFrog modes, i.e. as Refreshers, Quizzes, and LUs.

General question architecture and deployment

An example of a question connecting two KEs is **"Disease X may develop following a treatment with:"** (Figure 18). One of the drugs linked in the database as predisposing to indication (disease) X is selected randomly as the best ("correct")[11] answer option. Three incorrect answer options (distractors) are randomly compiled from the list of drugs not predisposing to disease X.

Both single and multiple-choice questions can be answered only once during a given question presentation, i.e. there is no option of going back and correcting wrong answers. Option selection is followed by an automatic answer verification screen (Figure 19 and Figure 20):

- In case of a correct answer, the best option(s) is (are) tagged green.
- In case of a wrong answer, the best option(s) is (are) tagged green and the incorrectly chosen option red (Figure 19 and F. 20).
- Book icons on the answer bars provide reference, i.e. access to the four KEs from which the options are derived (Figure 19 and Figure 20). When deployed within a Quiz, or as a Refresher, the verification screen additionally contains a "More information" button leading to the Drug or Indication card a given question is related to (Figure 19 and Figure 20).

[11] The terms "correct" and "incorrect" are used in the following as they are more intuitive.

Answering a question affects the user's proficiency in the KE this question is derived from; in the above example that of the Indication subsection Etiology. The concept and details of proficiency calculation are described separately under Adaptive learning.

The question headers contain no names of the drugs and indications they are derived from, because they would provide answers to some questions.

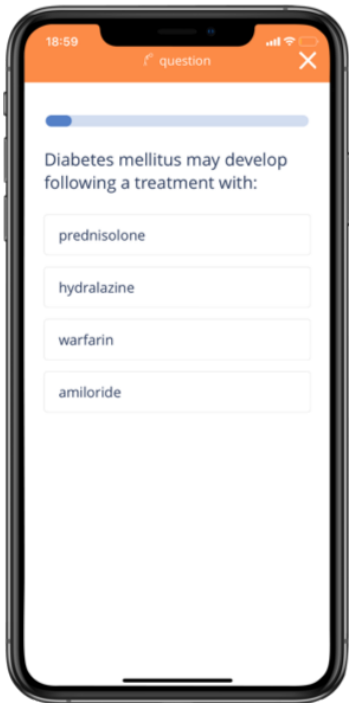

Figure 18: An example of an Indication-related, automatically generated question.

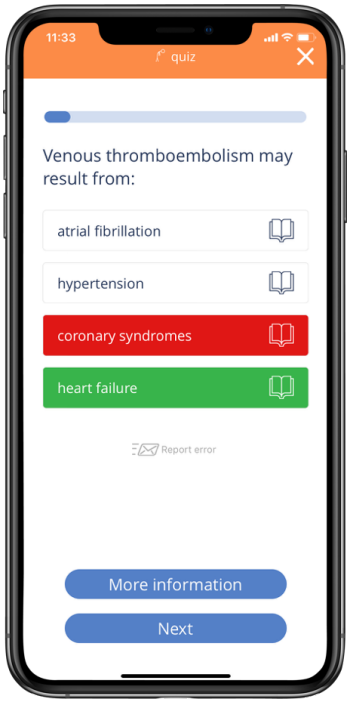

Figure 19: Example of a single answer choice question.

Figure 20: Example of a multiple answer choice question.

Identification of question templates

The aforementioned and further questions were identified through several discussion rounds between students and pharmacology experts. The general approach is described in the following for questions identified for Drugs, using the specific example of the antihypertensive drug ramipril. The seven ramipril-related data categories (Figure 21) can be summarized in the following sentence:

(1) Ramipril (2) inhibits the (3) enzyme (4) ACE which (5) reduces (6) arteriolar resistance and thereby modulates (7) cardiac output.

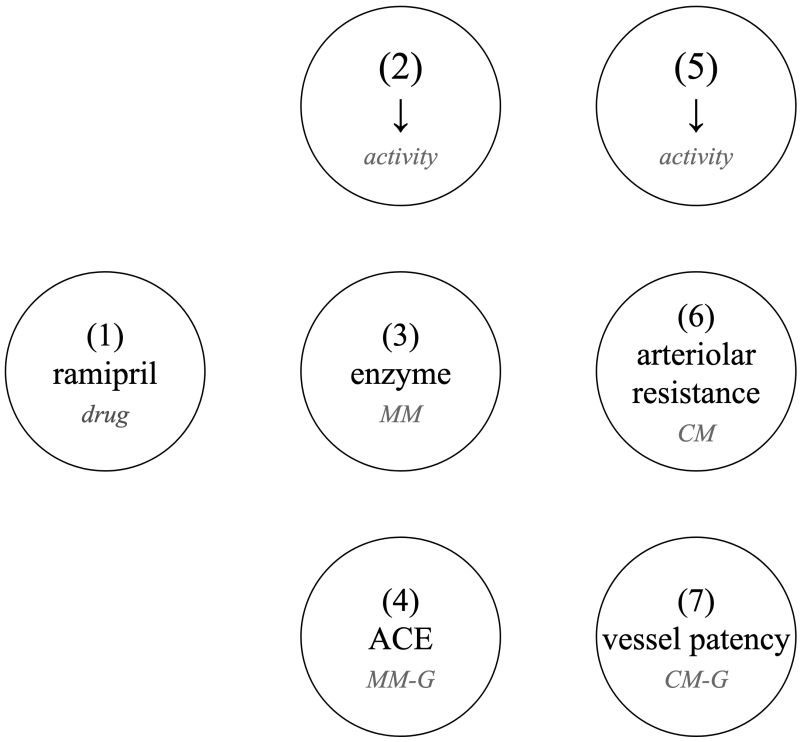

Figure 21: Drug-related KEs and other data using the example of the antihypertensive drug ramipril. MM - Molecular Mechanism, CM - Clinical Mechanism, MM-G - Molecular Mechanism Group, CM-G - Clinical Mechanism Group.

Discussion participants then attempted to identify all connections (Figure 22) resulting in short, understandable, and answerable question prompts (Table 6). The application of these questions to ramipril is presented in Appendix C.

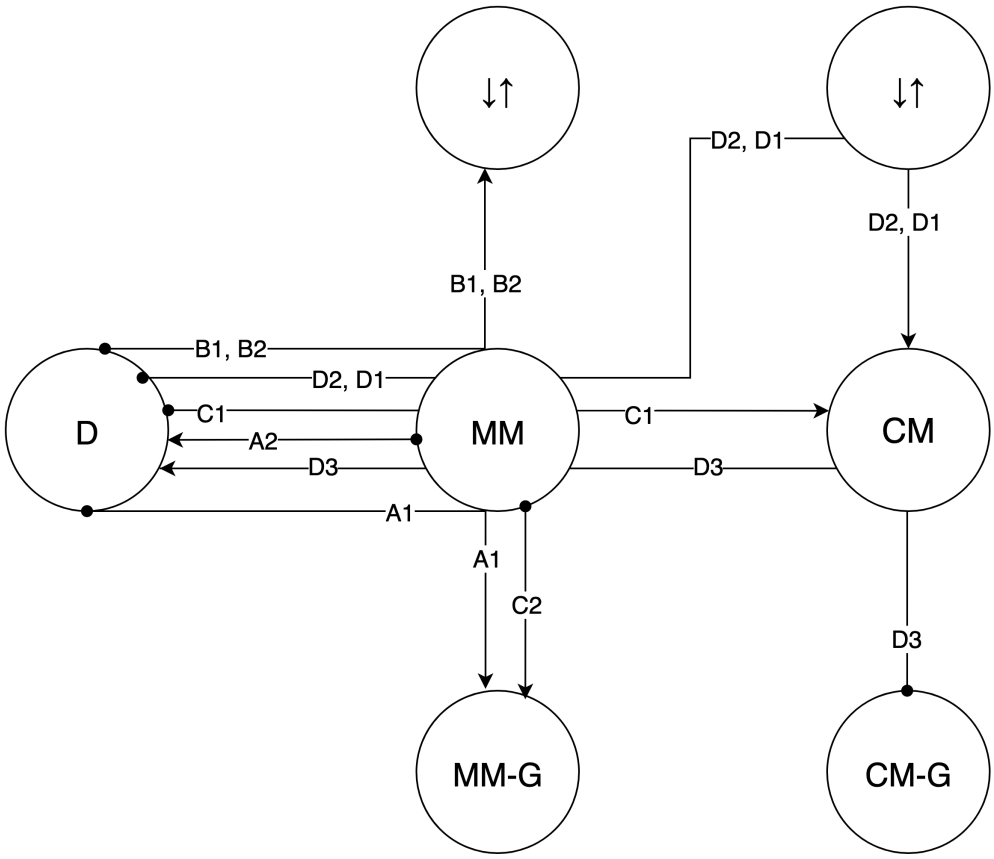

Figure 22: Connections among KEs and other data used to create Drug-related questions.

No.	Question prompt	Option categories
A1	The DRUG target MM belongs to:	MM-G
A2	To modulate the activity of MM I deploy:	D
B1	What is the effect of D on MM?	↑↓[increase/decrease] activity
B2	I deploy D to ↑/↓ [raise/lower] the activity of:	MM
C1	Targeting MM with D will affect:	CM
C2	Changes in CM in response to D will affect:	CM-G
D1	To ↑/↓ [raise/lower] the activity of CM I deploy:	D

D2	I deploy DRUG to:	↑/↓ [raise/lower]CM
D3	An adequate CM can be assured with:	D

Table 6: Generic forms of Drug-related question prompts and answer option categories

An analogous strategy applied to KEs and other data related to Indications identified question prompts and answer option categories presented in Table 7. The application of these questions to the indication hypertension is presented in Appendix D.

No.	**Question prompt**	**Option categories**
A1	In which patient would you suspect INDICATION?	case scenario
B1	INDICATION may develop following a treatment with:	D
B2	INDICATION may result from:	INDICATION
C1	Untreated INDICATION may lead to:	INDICATION
D1	Which of the following may be disturbed in INDICATION?	CM
F1	For prevention of INDICATION I deploy drugs that:	CM
F2	For prevention of INDICATION I deploy drugs that:	MM
F3	For prevention of INDICATION I deploy:	D
G1	For cure of INDICATION I deploy drugs that:	CM
G2	For cure of INDICATION I deploy drugs that:	MM
G3	For cure of INDICATION I deploy:	D
H1	For course modification of INDICATION I deploy drugs that:	CM
H2	For course modification of INDICATION I deploy drugs that:	MM
H3	For course modification of INDICATION I deploy:	D

J1	For symptom relief of INDICATION I deploy drugs that:	CM
J2	For symptom relief of INDICATION I deploy drugs that:	MM
J3	For symptom relief of INDICATION I deploy:	D
K1	Select a treatment goal for INDICATION that is achievable with pharmacotherapy	Therapy goals

Table 7: Generic forms of Indication-related question prompts and answer option categories.

Thus, identified questions underwent extensive in-app testing, in some cases resulting in revisions. For example, the Drug-related question "By deploying DRUG I: (↓ or ↑ the activity of a CM)" was changed to: "I deploy DRUG to:". The change clarifies that the deployment effect was intended, as opposed to unintentional effects such as ADR.

Another revision example is the Drug question "The activity of the bisoprolol target adrenoceptors affects: (a CM, e.g. myocardial contractility). The question had been meant to interrogate the CMs affected by bisoprolol: myocardial contractility, heart rhythm and heart rate. However, in the above form, it interrogated CMs affected by all adrenoceptors, i.e. additionally arteriolar resistance (reduced by urapidil via alpha1 and methyldopa via alpha2 adrenoceptors), and airway resistance (reduced by salbutamol via beta2 adrenoceptors). This problem was corrected by narrowing the scope of adrenoceptors interrogated by the question through rephrasing to: "Targeting MM1 (adrenoceptors) with DRUG1 (bisoprolol) will affect:".

Question and option exclusion

Excluding questions and answer options had to be implemented in the app code for various reasons and in two different ways.

Automatic exclusion:

- **Option exclusion:** Early on, it was decided to deploy whenever possible single- rather than multiple-choice questions. However, the nature of the topic covered (pharmacotherapy) results in many questions having more than one best answer option. Thus, many MMs can be modulated by more than one Drug (Drug question B2, Table 6). Likewise, some untreated Indications may lead to multiple other Indications (Indication question C1, Table 7). For example, hypertension may result, among others, in both coronary syndromes and heart failure. To solve this problem, the pertinent questions have been programmed to

permit only one, randomly chosen correct option. Simultaneously, the other correct options are automatically excluded from distractors.

- **Question exclusion:** Disease biology and/or pharmacology occasionally invalidate questions. For example, Chagas disease, an infection, obviously lacks predisposing indications, which invalidates question B2 in Table 7 for chagas disease.

Customized exclusion:

- **Option exclusion:** This was driven by the peculiar biology, particularly among MMs, i.e. drug targets. Thus, the Na^+/K^+-ATPase is both an enzyme and an ion transporter. However, the current app architecture permits assigning MMs only to one MM-G. The problem was solved by classifying the Na^+/K^+-ATPase as a transporter[12] and customized exclusion of enzymes from the distractor list. A similar strategy was applied to adrenoceptors which, depending on the drug, may undergo either activation or inhibition. One of these outcomes was excluded from the correct options and from distractors of the pertinent questions.

- **Question exclusion:** This refers to excluding entire questions through exclusion of elements contained in the question stem. For example to exclude the drug question A1 'The ramipril target ACE belongs to:' both ramipril (Drug) and ACE (MM) elements will have to be manually excluded for question A1.

Feedback

Sending feedback can be considered a special form of interactivity. PharmaFrog app users can send feedback about errors in SHOW ME cards and in questions. The feedback editor (Figure 23 A) for SHOW ME cards is available via the side menu. The message sent automatically includes a reference to the card the feedback is about. Feedback to questions can be sent directly from question screens (Figure 23) via 'Report error' link.

.

[12] The transporting function is more relevant for the understanding of this drug target.

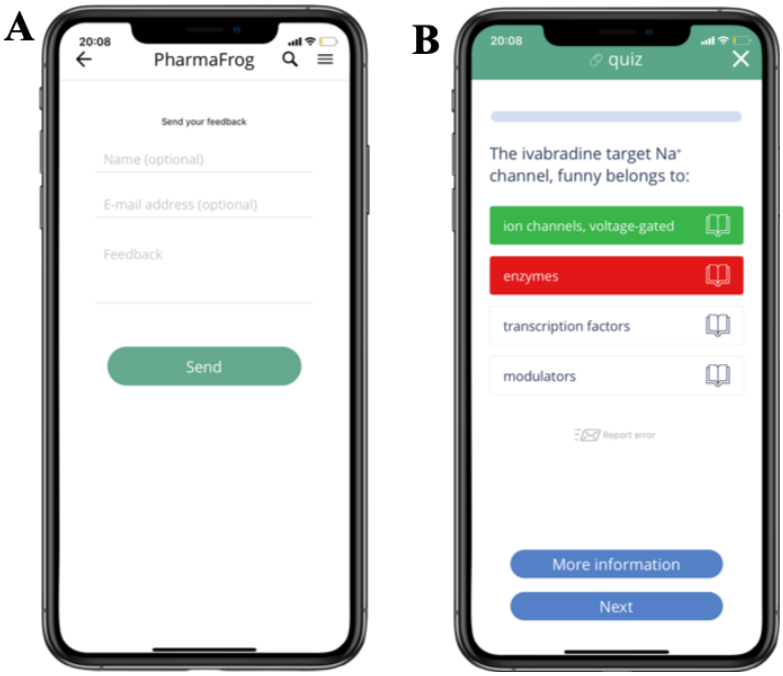

Figure 23: Feedback screens.

Personalization

Personalization means tailoring the app to the preferences and interests of individual learners. In PharmaFrog, personalization is implemented through the selection of the learning:

- mode
- pace
- scope

Choice of learning mode

PharmaFrog 2.0 features four learning modes: the already described, reading-based SHOW ME mode and three interactive, i.e. question-containing modes of increasing complexity: REFRESHERS, QUIZ ME, and TEACH ME. All learning modes but REFRESHERS[13] are accessible via the app dashboard (Figure 24).

These three interactive modes will be described in the following. At all times, users are fully flexible in the selection of the learning mode they prefer.

[13] Refreshers are generated and sent automatically.

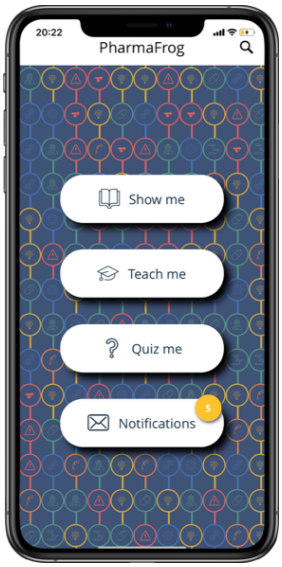

Figure 24: Learning modes.

Figure 25: Example of a refresher notification.

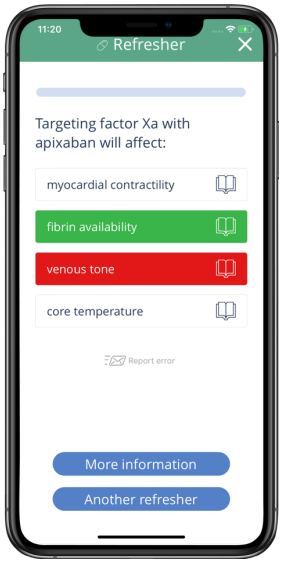

Figure 26: Example of a refresher question.

Refreshers

Refreshers are Drug- or Indication-derived daily[14] questions displayed to users and opened in a way similar to WhatsApp notifications (Figure 25). Clicking on the notification opens the Refresher within the app (Figure 26). Each answered Refresher contains a "More information" button which opens the Drug card (for drug related questions) or KE card (for Indication related questions) the question just answered is derived from.

Quizzes

Quizzes are accessible via "QUIZ ME" (Figure 24) and constitute a series of 10 questions each. Each answered Quiz question features a "More information" button which opens the Drug card (for drug related questions) or KE card (for Indication related questions) the question just answered is derived from. A progress bar gives feedback how far a user has advanced with the Quiz.

Learning Units

Learning Units (LUs) are deployed via TEACH ME (Figure 24) and constitute the most complex learning mode of the PharmaFrog app. In the app version 2.0 they are available for Indications and Drugs, in line with the analysis of PharmaFrog 1.0 user needs assessed through user journeys described in SHOW ME deployment section.

[14] By default. The frequency can be changed to weekly or no Refreshers at all in the app settings.

Briefly summarized, LUs consist of KEs that form an Indication or a Drug card. The sequence of KEs in Indication LUs follows their sequence in Indication cards in the SHOW ME mode of the app.

Drug-derived LUs present KEs constituting a given drug's MMs and CMs, beginning with the normal function of a MM (drug target), through its therapeutic modulation, to normal function and therapeutic modulation of the related higher order physiological mechanism (CM).

In either LU type, each KE is followed by 1-3 questions derived from and interrogating this KE (section: general question architecture). The questions verify whether the immediately preceding KE has been understood and/or retained. This principle results in LUs being a series of KEs interspersed with questions, as depicted in detail in the Appendix C for the drug ramipril and for its major indication hypertension in the Appendix D. A progress bar gives feedback how far a user has advanced with a given LU. The LU architecture is summarized and compared in Table 8 to those of the other learning modes of PharmaFrog. For example, KEs are included in all activities, in SHOW ME and TEACH ME as default, and in QUIZ ME and Refreshers as optional items accessible via book icons on the answer bars and via "More information" buttons.

The app currently features no questions interrogating the Indication KE "Signs & symptoms". Further, some KEs lack questions for certain Indications. For example, Chagas disease, an infection, obviously lacks predisposing indications, which invalidates question B2 in Table 7. In all such cases, the pertinent KE is simply followed by the next KE in the LU sequence.

Learning mode	**Components, sequence and length**
SHOW ME	$KE_1, KE_2, KE_3, \ldots, KE_n$ (n=4 for drugs and n=9 for indications)
TEACH ME	$KE_1+Q_1+Q_2+ Ke_2+Q_3+Q_4 +, \ldots , KE_n+Q_y+, \ldots, +Q_x$ (n as above)
QUIZ ME	$Q_9(+KE_9), Q_5(+KE_5), \ldots, Q_n(+KE_n)$ (n=10; lookup of Ke optional)
Refreshers	$Q_7(+KE_7)$ optionally $Q_9, Q_5, \ldots Q_n$ (n= ∞.; lookup of KEs optional)

Table 8: The composition and sequence of the individual learning-promoting activities.

Indication LUs currently contain nine questions, as do the 80% of PharmaFrog drugs that act via a single MM affecting a single CM (Figure 27, panel A). The other 20% drugs have either multiple MMs, or multiple CMs (panels B, C, and D). Panel E represents the hypothetical, most complex MM-CM relationship that could arise.

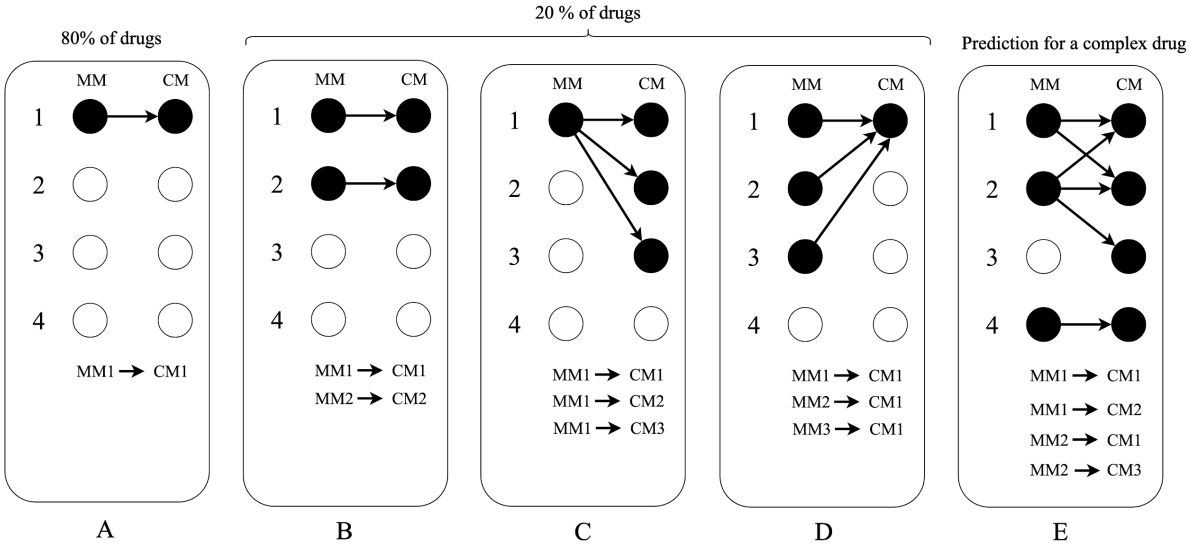

Figure 27: The schematic representation of MM and CM relationships.

To accommodate this diversity, the following two rules were developed:

1. Each Drug LU starts with a MM and continues with CM → MM → CM… , i.e. MMs and CMs are presented interchangeably.

2. A given MM is shown only once within a given LU. This rule shortens LUs to a reasonable length and eliminates potentially irritating redundancies.

When deployed within LUs, KE are preceded by cues i.e. short automatically generated messages addressing the learner (Figure 28 A). The messages summarize the material just covered and connect it with the upcoming one. The resulting narrative strives to help connect KEs into a story, thus facilitating understanding and reducing LU terminations. The narrative form tries to create the impression of a Mario-like mentor gently whispering into the learner's ear.

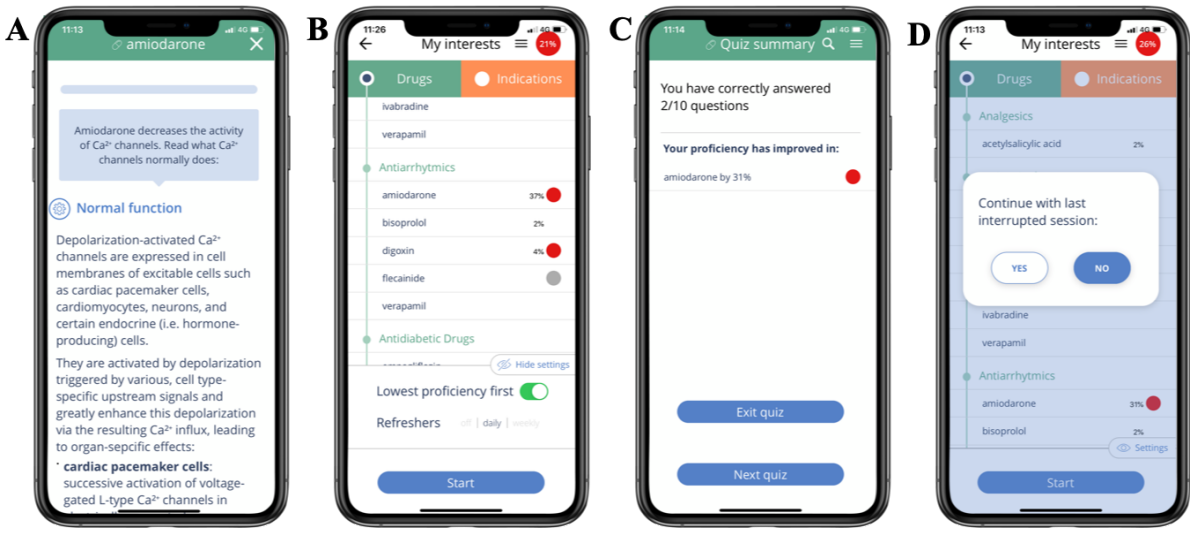

Figure 28: Sample screenshots from LU.

Choice of learning pace

As PharmaFrog is fully functional offline, users can freely choose their individual learning pace as long as their smartphones are charged and turned on. In addition, PharmaFrog offers the following features individualizing the learning pace:

- **Refresher frequency:** by default, Refresher frequency is set to one per day. This can be modified in the learning scope selection screen (Figure 28 B) to one refresher per week, or none at all.
- **Refresher time-point:** refreshers are deployed at intervals of 24 hours. By delaying answering a refresher, a user can create a preferred time-point for deploying them.
- **Refresher length:** users are expected to answer at least the one question they are notified about, but they may continue with further questions. Alternatively, they may decline the refresher, in which case the same question will be deployed again after 24 hours (or 1 week, depending on the set time interval).
- **Quiz early termination:** users may terminate a Quiz before they have answered all 10 questions. The results will be recorded for the questions answered before termination.
- **Quiz continuation:** having answered all 10 questions of a quiz, users are prompted and may choose to continue with another quiz (Figure 28 C).
- **LU interruption:** users may interrupt LUs at any time by closing the app or by switching to the reference mode SHOW ME. The results for the questions answered before

interruption will be recorded. Upon return to the TEACH ME mode, users may choose between continuing the interrupted LU and starting a new one (Figure 28 D).

Choice of learning scope

The set of downloaded KEs is the same for all PharmaFrog users. While using the app in the reference mode SHOW ME, users determine their learning scope through a fully autonomous choice and navigation through app cards and KEs.

My interests

For the interactive, i.e. question-containing modes TEACH ME, QUIZ ME and REFRESHERS, users may additionally select a specific subset of Drugs and/or Indications. This is done on the page "My Interests" (Figure 29 C), which is displayed upon each access of TEACH ME or QUIZ ME modes from the dashboard or from the side menu of the app. The selection is carried out through tapping on the individual Drugs and Diseases, or on the names under which they are grouped. Drugs are grouped according to how they are used, e.g. as analgesics or antianginals, Indications according to the affected organ system, e.g. circulatory & lymphatic, digestive, or endocrine. The selected Drugs and Indications feature colored dots (Figure 29), with colors representing the momentary proficiency. In the same manner and at any time, users can reduce, expand, or completely change their individual learning scope. The scope of Drugs and Indications selected at any given moment determines the scope of Refreshers, Quizzes and LUs.

Summary pages

Having initially selected Drugs A, B and C for learning and completed the LU for Drug A[15], the LU Summary Page prompts the user to continue with the next selected item of the same category, i.e. with the LU for Drug B (Figure 29 A). Importantly, the Page presents the list of Indications Drug A is used for. At this stage, the user can switch from learning Drugs to learning Indications treated with the Drug he or she has just become acquainted with. Conversely, having completed the LU for Indication A, a user may switch to the Indication A-related Drug X rather than continue with Indication B (Figure 29 B).

[15] Later on, the order of LUs will be driven not by the alphabetical order but by proficiency, with Drug or Indication LUs with the lowest proficiency deployed first.

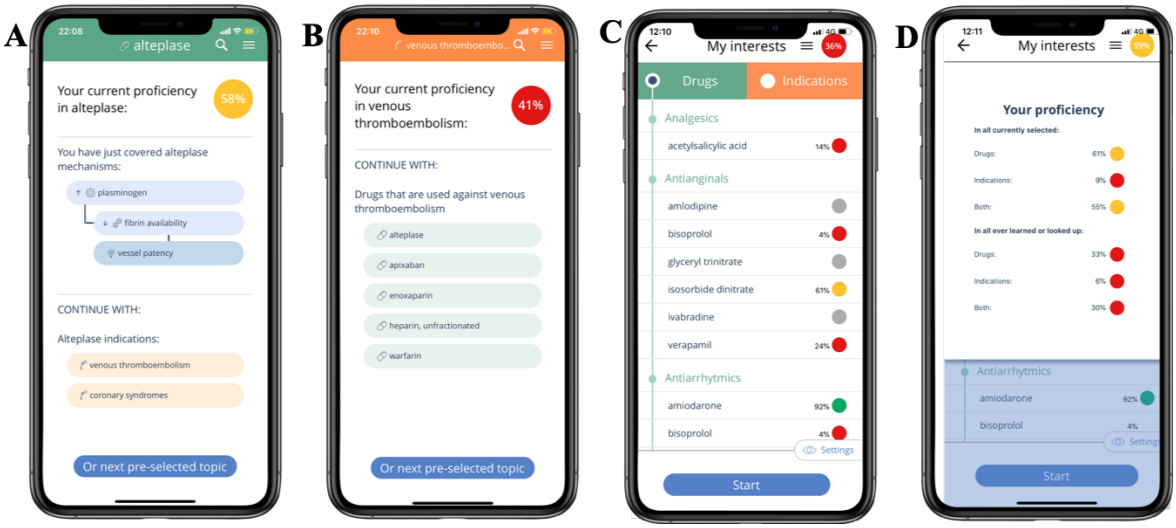

Figure 29: Proficiencies in (A) Drug and (B) Indication LU, in (C) My interest and (D) in the aggregated proficiency view.

Search

The search function enables quick access to the content a user is interested in. PharmaFrog utilizes an SQLite-based search algorithm. It uses a special column in the 'articles' table in the SQLite database that was added extra to store the information as plain text. The user types the information they are searching for into the search window. Different articles in which that information is contained are displayed with the search term(s) bolded. The articles are sorted according to the major SHOW ME categories.

Adaptive learning

The adaptation of learning to the content difficulty and the learner's ability is a key determinant of the learning outcome. PharmaFrog offers adaptive learning based on the concept of proficiency.

Proficiency definition and measurement

Proficiency is defined as a dynamic estimate of knowledge and skills resulting from all four learning-promoting activities. Briefly summarized:

- **Primary proficiencies are measured and recorded** at the level of the individual questions associated with a given KE. Primary proficiencies remain hidden from the user. Questions with the lowest primary proficiency among all questions related to the present learning scope are by default selected for presentation in Quizzes and Refreshers. Otherwise, primary proficiencies are used for the calculation of Drug and Indication proficiencies.

- **Drug and Indication proficiencies** are averages of primary proficiency values for all questions associated with a given Drug or Indication. They are displayed on the summary pages of completed LUs (Figure 29 A and B for Drugs and Indications respectively), and permanently on the learning scope selection screen (Figure 29 C). Drugs and Indications with the lowest aggregate proficiency values among all Drugs and Indications constituting the present learning scope are by default selected for presentation as LUs.

- **Aggregate proficiencies** (Figure 29 D) are averages of proficiencies of all Drugs and/or Indications:

    - constituting the current learning scope

    - ever looked up via SHOW ME and/or interactively learned via TEACH ME, QUIZ ME, or REFRESHERS, irrespectively of the current learning scope.

Proficiencies range from 0 to 100%. Drug and Indication proficiency values >0% are presented in the learning scope page irrespectively of the selection status. Proficiencies of Drugs and Indications within the current learning scope are additionally visualized in the app using the traffic lights code, with **red** signifying **insufficient (0-49%)**, **yellow** moderate **(50-79%)**, **green** sufficient **(80-100%)** proficiency. **Grey** dots depict Drugs and Indications included into the learning scope, but not yet learned.

The proficiency in Drugs and Indications within the present learning scope by default drives the selection of questions for Quizzes and Refreshers, and of Drugs and Indications for LUs. Specifically, questions and Drugs and Indications with the lowest proficiency values are deployed first.[16] In consequence, users are preferentially exposed to questions and LU which they encounter for the first time, or which they are estimated to be less familiar with. This estimate is based on an algorithm predicting proficiency decline.

Proficiency values are automatically saved and stored in the app. For registered users, they are additionally transmitted to the server. This enables the restoration of the learning status following the loss of the old, or the purchase of a new smartphone.

Proficiency generation

The proficiency level is a composite result of all four learning-promoting activities of PharmaFrog. Within the three interactive learning activities, i.e. TEACH ME, QUIZ ME, and REFRESHERS, the proficiency changes, and is recorded, on the level of the individual questions according to how they are answered (Figure 30). It raises from the initial value of 0%:

[16] Users may replace in Settings the “lowest proficiency first” with a random deployment of questions and LUs from the selected scope.

- to 100% upon selection of the correct answer option
- by 30% upon selection of a distractor, but followed by reading any of the KEs linked via book symbols in the bars with answer options. The value of 30% was selected arbitrarily, based on the assumption that a substantial learning effect is achieved through inspection of the correct answer combined with reading the linked, explanatory information.
- by 10% upon selection of a distractor, but declining to read any of the associated further information. The value of 10% was selected arbitrarily, based on the belief that a certain learning effect is achieved through inspection of the correct answer.

Furthermore, proficiency increases also upon accessing Drug or Indication cards via the SHOW ME mode of the app. In this case, all[17] questions related to a given card are assigned a 2% proficiency increase. This results in a 2% increase of proficiency aggregated on the Drug or Indication level. The SHOW ME-driven proficiency increase is kept this low, since the reading time and intensity of the Drug and Indication cards are at present unknown.

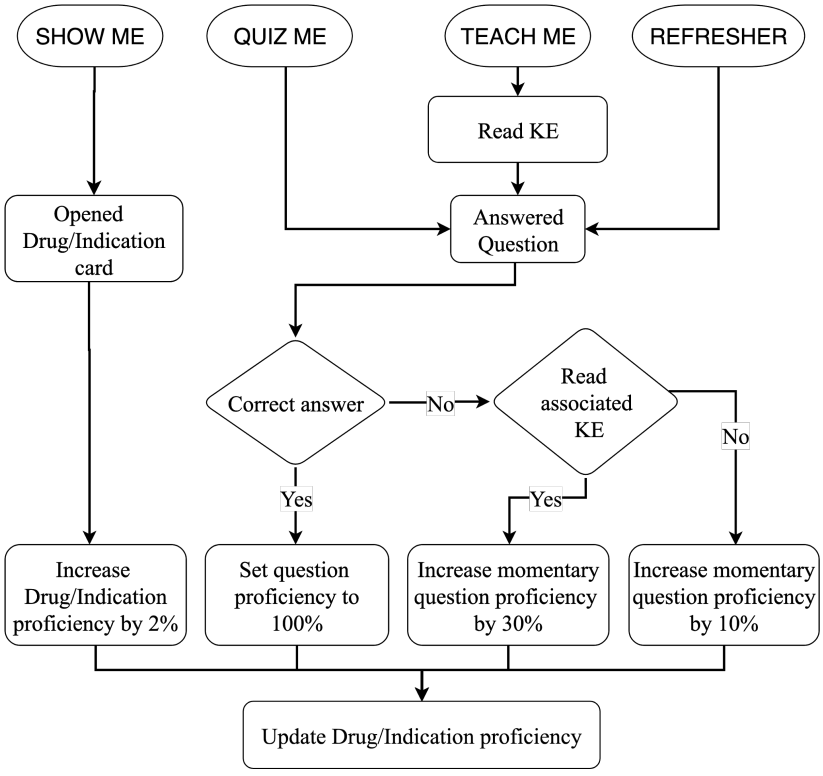

Figure 30: The effect of the outcomes of the four different learning activities on the proficiency levels in PharmaFrog 2.0.

[17] The SHOW ME-derived proficiency increase benefits all questions associated with a given Drug or Indication, because PharmaFrog currently cannot detect which specific KEs have been read.

Proficiency fine-tuning

To provide a remedy for the aforementioned uncertainty regarding the contribution of the reading time and intensity to proficiency, a concept was developed for a future app version. The SHOW ME-derived proficiency will consider the estimated completeness of KE reading. The completeness estimate itself will be calculated using the time spent reading a KE, the number of words in this KE, and the individual reading speed. A fuller description of this concept is provided as Appendix H.

Proficiency decline

To emulate forgetting, proficiency values associated with PharmaFrog questions decline exponentially with time using the formula:

$$y_c = y_l(1-r)^x$$

where:

y_c = the *current* proficiency

y_l = the proficiency after the last learning-promoting event

r = the current forgetting coefficient

x = the number of days since the last change of the forgetting coefficient r

The initial forgetting coefficient r is preset to 0.015469. This r value results in halving an initial proficiency value of 100% within approximately 6 weeks (Figure 31). The r value may undergo the following adjustments under subsequent knowledge retrieval (verification) events:

- halving to 0.007734 following a **correct** question answer: the proficiency in the above example will halve no longer after 6 weeks but after approximately 3 months
- doubling to 0.030938 following an **incorrect** question answer:[18] The proficiency in the above example will halve already after approximately 3 weeks.

[18] An exception is the first incorrect response, upon which the r value remains unchanged. This is meant to exclude the risk of frustrating users with a flood of questions, in case they turn out to be too challenging rather than too easy.

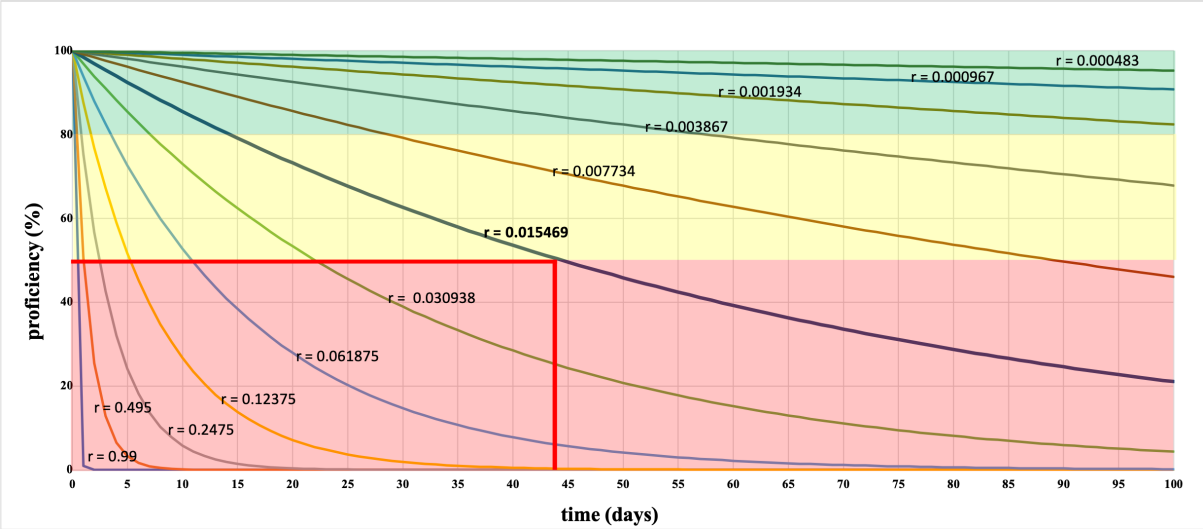

Figure 31: Forgetting curves as a function of the forgetting coefficient r.

Questions difficult to answer will experience faster proficiency declines than easier questions. As already mentioned, questions and LUs with the lowest proficiency values are the first ones to be deployed, respectively, as Refreshers and Quizzes, and as LUs. This relationship forms the basis for the proficiency-based adaptive learning concept implemented in PharmaFrog as described in the following.

Adaptation scenarios

Adaptive learning is deployed in the three interactive learning modes of PharmaFrog: TEACH ME, QUIZ ME and REFRESHERS. Briefly summarized, learners are first presented with content they have difficulties with due to:

- their particular learning capacity
- the difficulty level of the individual KEs and/or of the derived questions.

Normally, the selection of LUs and of questions for Quizzes and Refreshers is based on the current proficiency values: LUs and questions with the least proficiency are presented first. For an easier understanding, assume that LUs and questions are triggered instead when proficiency undercuts 50% (Figure 32).

To learner's capacity

Learners' capacity for knowledge retrieval undergoes a pronounced inter- and intraindividual variability. The upper panel depicts the performance of Student A, the lower panel that of Student B. Both students are motivated to learn, but Student A has a better knowledge retrieval capacity than Student B. Alternatively, these panels may represent one and the same student assessed at two

different time-points, reflecting intra- rather than interindividual variability in learning performance.

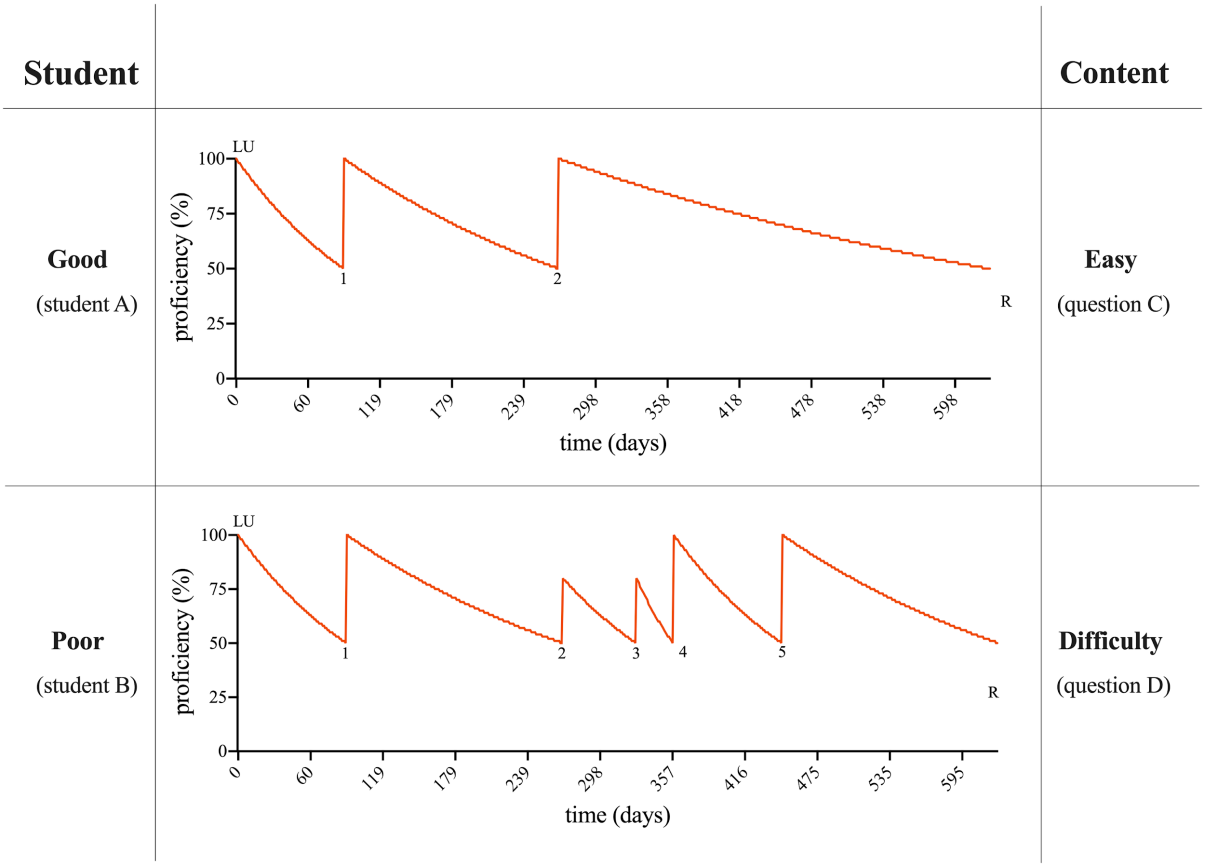

Figure 32: The course of proficiency as a function of content difficulty and of student performance.

Both students correctly answer a question presented within a selected LU: The proficiency is set to 100%, but begins to decline at r=0.007734.[19] After some 3 months, both proficiency values undercut 50% and both students are prompted to answer a Refresher with the same LU question.[20]

- Student A correctly answers this and later yet another Refresher with the said question. The forgetting coefficient r halves with each correct answer. In consequence, the forgetting curve flattens and the intervals between upcoming Refreshers become longer.
- Student B performs in a less consistent way. The first Refresher is answered correctly, the subsequent two are not. In consequence, the initial halving of the forgetting coefficient r is

[19] The halved standard initial r of 0.015469.

[20] In the context of a LU, this would be typically the first LU question, i.e. the one which was answered first when taking the LU and, accordingly, first undercut the set proficiency threshold of 50%.

offset by two doublings and *r* is now set to 0.030938. Following each failed Refresher Student B reads the KE the Refresher is derived from, which each time boosts the proficiency to 80%. Refresher 4, triggered only 1 month after Refresher 3, is answered correctly, as is Refresher 5.

Taken together, the algorithm adapts the intensity of learning to the individual knowledge retrieval capacity. Both students ultimately develop similar long-term memory of the knowledge interrogated by the question, as indicated by the long-time trend towards low forgetting rates. Student B simply needs more interactions over a longer period of time to master the material.

To content difficulty

Upon replacement Students A and B by questions C and D, (Figure 32) depicts the adapting to differences in question/KE difficulty. Question/KE C is apparently easier and requires less repetitions, question D is more difficult and requires more.

Overview of PharmaFrog 2.0 navigation hierarchy

To facilitate understanding, the top-down navigation through all learning modes and Notifications can be divided into four levels presented in Table 9.

	Hierarchy levels			
	I	II	III	IV
SHOW ME	HOME	Dashboard	Various lists	Content cards (KEs)
TEACH ME		My interests	Lists of Drugs & Indications	KEs & Questions
QUIZ ME		My interests		Questions
NOTIFICATIONS		-	List of Notifications	Notifications
REFRESHERS	-	-	-	Questions

Table 9: The hierarchy of navigation through PharmaFrog 2.0.

PharmaFrog 2.0 evaluation

PharmaFrog app was shared with potential users via mailing lists and social media, specifically via Facebook and WhatsApp. Additionally, the app was presented in short discussion groups and class sessions of maximally 15 minutes to students and faculty members at 4 medical schools and two pharmacy schools in Tanzania. Student leaders and faculty members of the six visited schools were approached to help share the app with the students via other channels such as local social media groups and learning management systems.

User acceptance

Survey results

A survey (Appendix E) consisting of 14 questions was compiled together with six pharmacology experts during an online IUPHAR workshop conducted in September 2019.

In order to collect feedback only from individuals who had actual app engagement, the link to the survey was embedded into the app. Users were prompted to take the survey after a total of 70 clicks. Thirty-one complete responses were received until March 11, 2019.

Participants description

Among the survey participants, 28 were from Tanzania and one from Rwanda, whereas two did not state their location. A majority of the respondents (58%) were students. Medical doctors, pharmacists and educators accounted for the remaining 42%. (Figure 33).

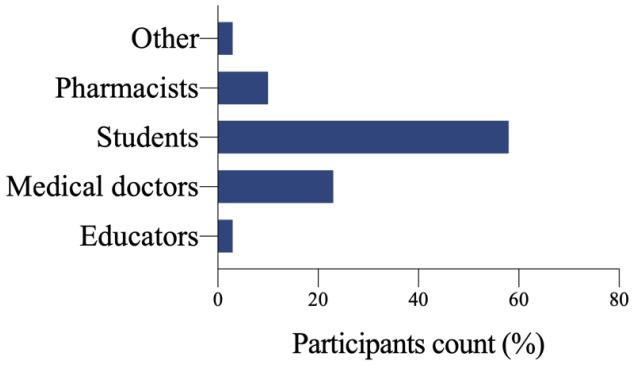

Figure 33: Survey participants by profession.

Among student participants, 70% were students of medicine, 18% pharmacy students, and 12% postgraduate students (Figure 34 A). All student respondents had some knowledge of pharmacology. Indeed, 19% of students were in their second year of studies, a level at which basic

pharmacology is taught in Tanzania. Sixty-nine per-cent were fourth-year students, which coincides with the introduction to clinical pharmacology. The 12% postgraduate students must have already had some practical experience with drug prescribing (Figure 34 A).

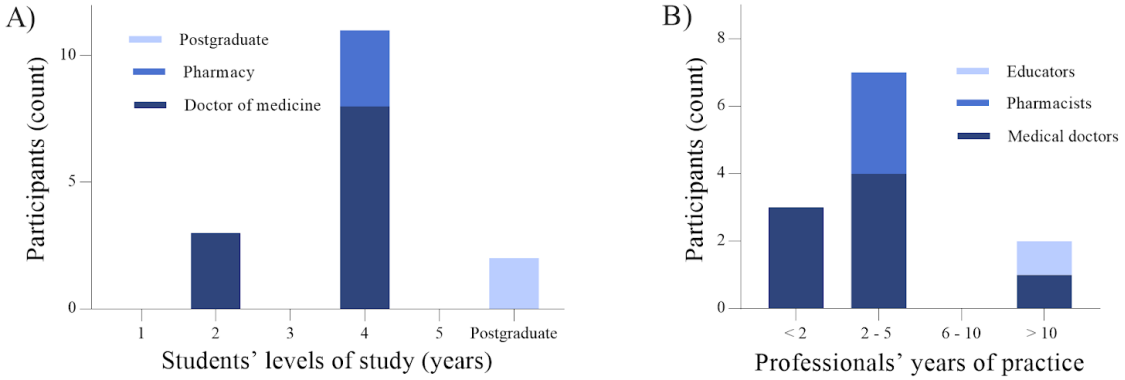

Figure 34: Survey participants according to (A) study period and (B) duration of practice.

Most of the practicing respondents had 0-5 years of work experience (Figure 34 B). Among them, 8 were medical doctors, including one for each of the following specialties: anesthesiology, emergency medicine, internal medicine, public health, oncology, and pediatrics. Three respondents were pharmacists, one was an educator, and one did not state their profession. Most of the practicing participants work in public institutions of tertiary level (Figure 35).

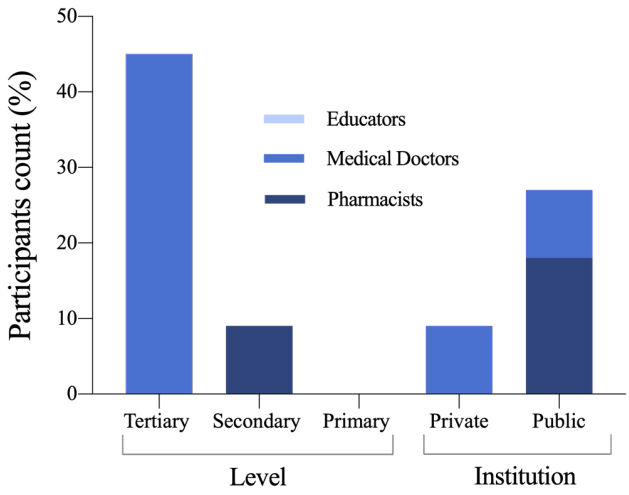

Figure 35: Study participants according to areas of practice.

How much time in total have you spent using PharmaFrog?

A majority of the responses were received from users who had spent 6 hours and less interacting with PharmaFrog (Figure 36 A). Every-second participant (52%) had spent less than one hour interacting with PharmaFrog.

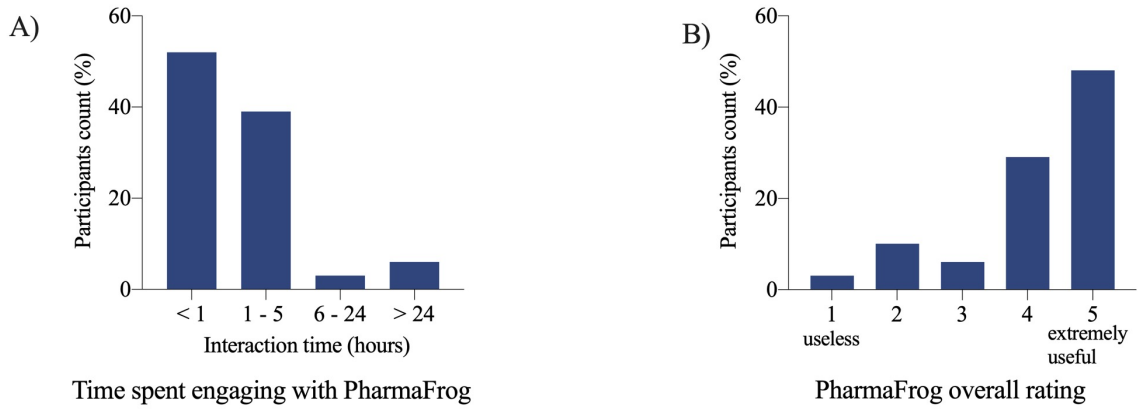

Figure 36: Interaction and rating of PharmaFrog.

What is your overall rating of PharmaFrog?

Respondents were asked to rate PharmaFrog on a of one to five. A score of four and five was interpreted as useful, 3 as neutral, two and one as useless. PharmaFrog was rated useful by the majority of the respondents (77%), as depicted in Figure 36 B.

Is PharmaFrog easy to use?

Respondents were required to answer 'Yes' or 'No' to this question. All participants (100%) found PharmaFrog easy to use. One of the participants commented *"It is easy app to use because is so directive like you are able to get a lot of information within one choice of drug"*.

Is the structure of PharmaFrog understandable?

Respondents were required to answer 'Yes' or 'No' to this question. All but one (96%) participants found the structure of PharmaFrog understandable. In comments, statements such as *"Understandable, simple, good"* were typically used to describe the structure.

Rate the amount of information per disease and drug in PharmaFrog.

A majority of the respondents (77%) found the information scope just right (Figure 37).

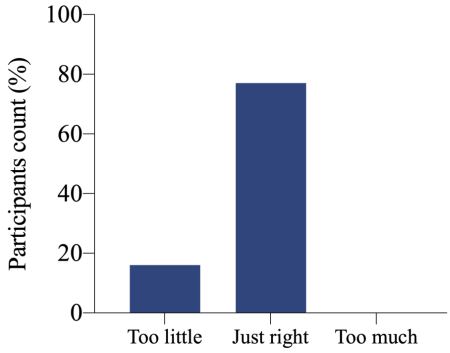

Figure 37: Rating of the current content density.

What would you add to PharmaFrog?

From comments, a majority of the respondents thought the already existing functionalities suffice the need, however some wished to add more case scenarios, app usage reports, medical pictures, and online quiz matches. For content, most suggestions were about increasing the number of Indications, specifically adding malaria, tuberculosis and cancer, and of Drugs, specifically adding antibiotics. One respondent commented *"Teach me everything, personalized drugs have to be at fingertips"*.

Would you recommend PharmaFrog to a colleague?

Respondents were required to answer 'Yes' or 'No' to this question. All respondents but one would recommend the app to a colleague. The one respondent who would not recommend the app, commented that the app *"still needs more information to be recommended"*.

Group discussions and interviews

Group discussions and interviews took place over a period of three weeks in December 2019 and January 2020 at four medical schools and two pharmacy schools in Tanzania. Medical students and students of pharmacy who already had knowledge of pharmacology (year two of study and above) and teachers of pharmacology were introduced to the app either via small group discussions or through in-class sessions. Altogether, the app was introduced to 12 teachers of pharmacology and 324 students.

Verbal feedback revealed that PharmaFrog was a very good app. Quoting some respondents;

- *"very good app, intelligently designed",* from a pharmacy lecturer
- *"clever idea",* from a deputy vice chancellor of academic affairs
- *"the already existing content is pretty good, I like the links, simple language, easy to understand",* from a head of pharmacology faculty of medicine.

Similarly, to what was revealed by the survey, the respondents recommended adding more content, especially to Drugs and Indications. There were suggestions to include drug interactions and contraindications, features that have already been considered for implementation in PharmaFrog but were not ready at the time of app publication.

A new interesting suggestion was to add pharmacokinetics to every drug card, to show how the drug is eliminated by the body, including the metabolic pathway, and elimination path.

App store ratings and reviews

The results for 3 months of use (December 11-31, 2019, January and February 2020, March 1-10,2020) were collected on March 11, 2020. The Android app had 310 total installations. The app had an average rating of 4.8 stars out of five. The iOS app had 164 installations with an average rating of 4.6 stars out of 5. Similarly to the survey, the app received positive feedback and there was thirst for more content exemplified by the comment from one of the app reviewers " Nice app...just add more content please".

App usage statistics

The following section is based on PharmaFrog 2.0 usage statistics from January 11, 2020 (after the app introduction sessions in Tanzania) through March 10, 2020.

Where are PharmaFrog users located?

PharmaFrog was downloaded in 28 countries and had a total of 1313 visits (Figure 38). A visit is a group of user interactions beginning with opening the app until stopping interacting for at least 30 minutes. Most visits were from Tanzania (39%), Germany (33%) and Poland (8%).

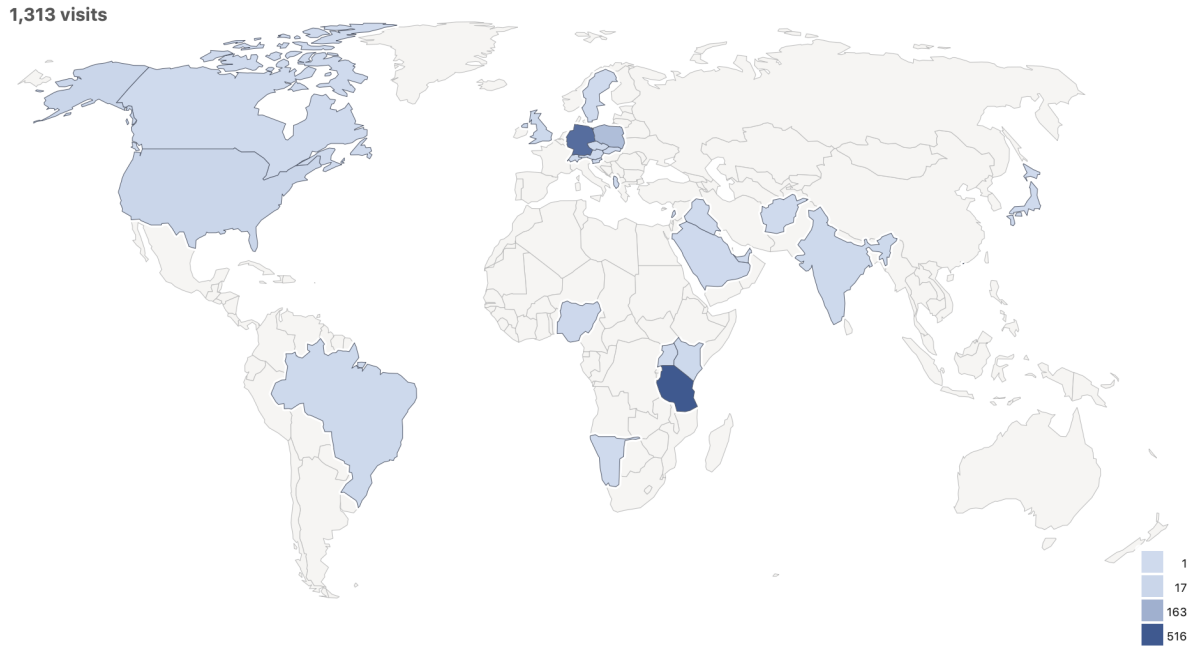

Figure 38: PharmaFrog 2.0 visits by country.

On average there were 22 visits per day. Each visit lasted on average four minutes and eight seconds. The distribution of visits throughout the day is shown in Figure 39, with late mornings (11:00 -12:00 hours) and late afternoon (16:00 hours) being the peak times.

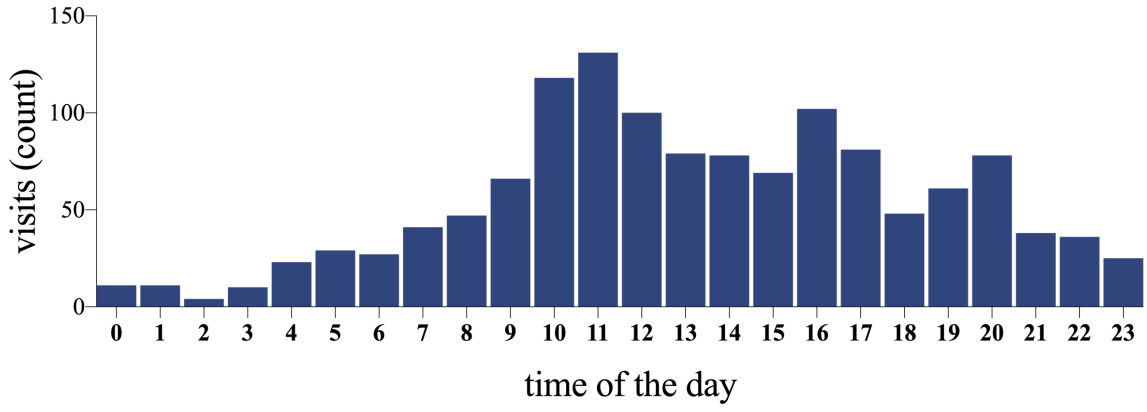

Figure 39: Visits to PharmaFrog 2.0 by time of the day.

What is the most used learning mode?

The most used learning mode was SHOW ME, accounting for 63% of user journeys that originated from the Home screen (Figure 40).[21] TEACH ME and QUIZ ME, reached through My interests screen, accounted for 20% of the traffic. Similarly to PharmaFrog 1.0, the most visited SHOW ME subcategory were Drugs, which were reached by 17% of the original journeys. They were followed by To consider (12%), Indications (8%) and the Library (10%).

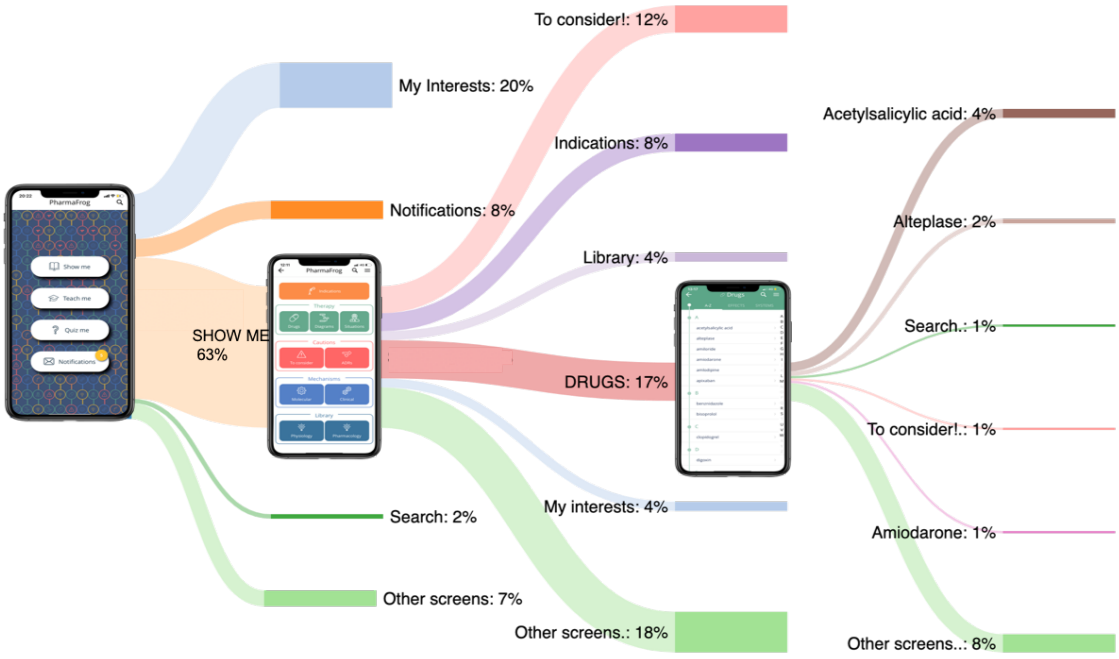

Figure 40: User journeys from HOME screen.

How do users navigate the app?

Users utilized the variety of navigation options provided in the app. Figure 40 exemplifies a hierarchical user navigation from the home screen i.e. from top category (level I as defined in Table 9) to content cards (level IV). Figure 41 depicts the navigation to and from level IV. Twenty-six per-cent of the traffic to the card 'coronary syndromes' came from the 'alteplase' card. Fourteen per-cent of the traffic went to the 'amiodarone' card. Ten per-cent of the traffic from the 'coronary syndromes' card went to Drugs, which is an example of navigation from level IV to level III (list level).

[21] All uphill (from right to left) and most inter-mode (e.g. TEACH ME to SHOW ME) and inter-category journeys (e.g. from a drug to an indication) are excluded for clarity.

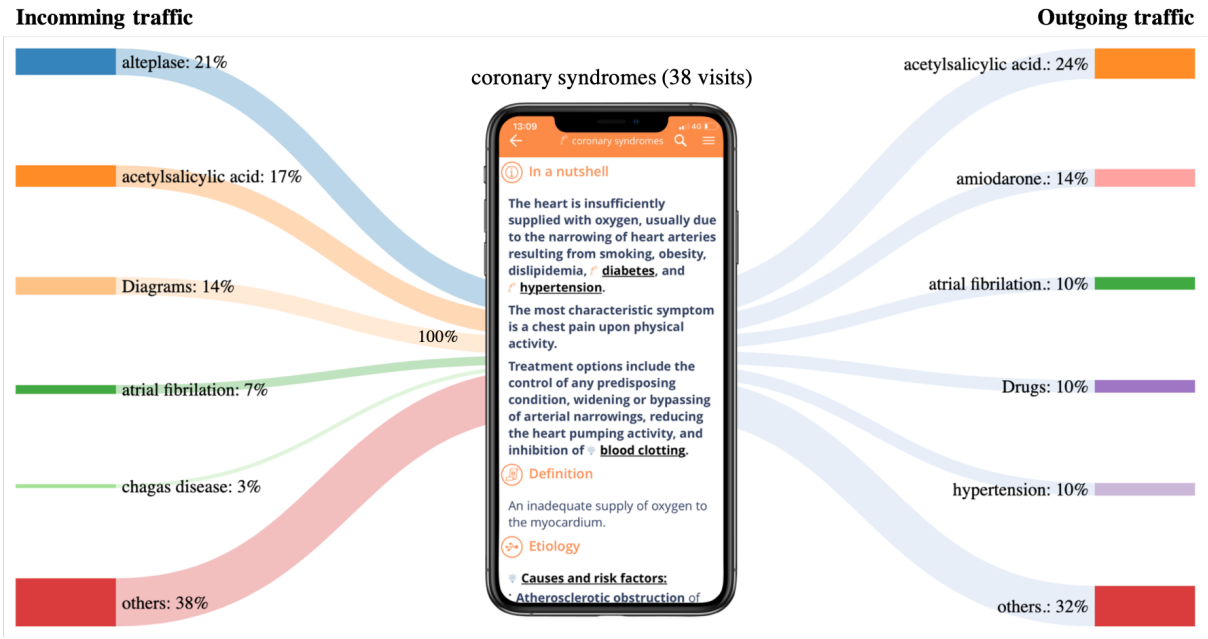

Figure 41: Incoming and outgoing traffic from an Indication card.

How were questions accessed?

TEACH ME, QUIZ ME and REFRESHERs learning modes share the same pool of questions. Therefore, they were evaluated based on the number of question attempts via each learning mode. Many early PharmaFrog testers and developers are based in Germany and Poland. To avoid bias driven by these countries, they were excluded from this analysis. An analysis of the remaining 774 user visits revealed 883 question attempts involving 198 unique questions. Most of the question attempts (82%) were through the QUIZ ME mode (Figure 42).

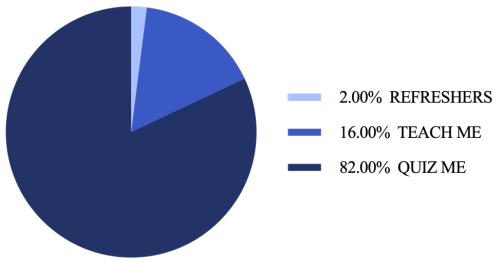

Figure 42: Question attempts per learning mode.

Average question reading time

Question reading time is defined as the time from when the question was opened to the time an answer was selected. The 4% of all question attempts made after 31 to 891 seconds were excluded from the following analysis.

The average reading and answering time of the remaining questions was 8 seconds. Seventy-six per-cent of the questions were read and answered within the first 10 seconds (Figure 43).

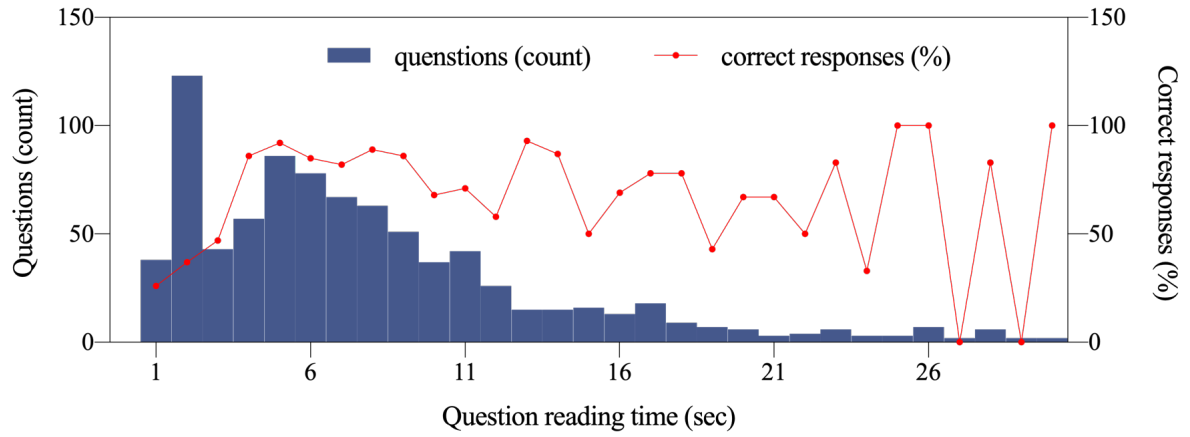

Figure 43: Distribution of number of question attempts and proportion of correct responses as a function of reading time.

The highest number of responses was registered within the second 2. Unsurprisingly - considering the short response time - only 37% of responses were correct. Similarly, poor performance was observed within the first and third second, with 26% and 47% of correct responses, respectively. The performance within the first second was practically identical to the 25% expected for random choices among the four available question options.

Thereafter, there was a steep increase to the peak of 92% correct answers in second 5 (Figure 43). Using two sample proportion Z-tests[22] at p-value <= 0.05 (Table 10), there was no statistical significance between the performances of the first and second, and between the second and third seconds. There was, however, a statistical difference when the proportions of the first three seconds (1", 2" and 3") were compared with seconds 4 and 5 ($p < 0.0001$). This result strongly suggested that the questions attempted within the first three seconds were answered correctly by chance, and that no learning effect could possibly have been achieved. Therefore, the first three seconds were excluded from the following analyses.

[22] The null hypothesis was that there were no statistically significant differences in the question answering performance among the time intervals tested.

Question attempts (count)	38	123	43	57	86
Correct responses (%)	26%	37%	46%	86%	92%
Time intervals	1st	2nd	3rd	4th	5th
1st			0.03495	<0.0001	<0.0001
2nd				<0.0001	<0.0001
3rd	0.03495			<0.0001	<0.0001
4th	<0.0001	<0.0001	<0.0001		
5th	<0.0001	<0.0001	<0.0001		

Table 10: Two-sample proportion tests for the question answering performance within the first five seconds. Tests with no statistically significant performance differences are marked grey.

The two-sample statistical test was then applied to grouped time intervals of 5 seconds (Table 11). The null hypothesis was as above. The proportion of correct responses in the first-time interval (4”-8”) was significantly higher compared to all time intervals, except during the last time interval tested (24’’-28’’). There were no statistically significant differences among all other group intervals. The proportions of correct responses gradually declined with time, again with the exception of the last time interval.

Question attempts (count)	351	171	71	26	21
Correct responses (%)	87%	75%	72%	62%	76%
Time intervals	4” - 8”	9” - 13”	14” - 18”	19” - 23”	24” - 28”
4” - 8”		0.000935	0.002632	0.001272	
9” - 13”	0.000935				
14” - 18”	0.002632				
19” - 23”	0.001272				
24” - 28”					

Table 11: P-values of two sample proportion z-test for grouped time intervals. Blue represents correct proportional samples at which statistical significance was observed, grey no statistical significance.

The impact of multiple question encounters

Most question attempts (75%) were first-time encounters with a given question (Figure 44). The percentage of questions answered correctly increased gradually for the first three encounters as depicted by the red line in Figure 44. For other encounters (4 to7) there were very few encounters and the performance was very unsteady (data not shown); therefore these results were excluded from the following analyses.

The null hypothesis was that the number of encounters with a given question had no effect on the proportion of correct answers. A two-sample proportion z-test revealed statistically significant differences between the first (76%) and the second (92%, P=0.000298), and between the first and

the third (94%, *P* value=0.007894) encounter. There was no statistical significance between the proportions of correct response of the second and third encounters. Altogether, this analysis demonstrated an improvement of the performance associated with question repetition, suggesting a learning effect.

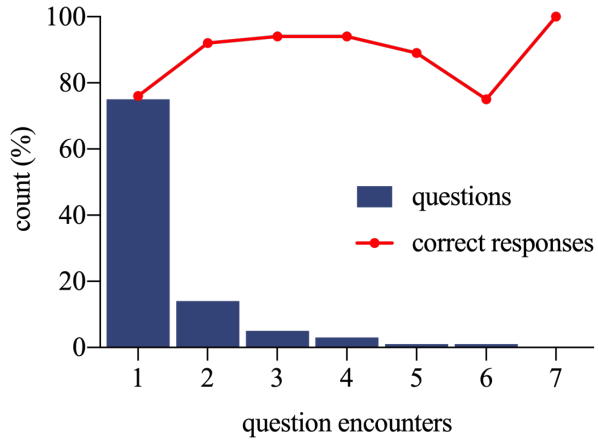

Figure 44: Question attempts as a function of number of encounters.

The possibility of a learning effect through repeated question encounters was then analyzed in more detail. This was done using combinations of three parameters: the encounter number, the answer correctness, and the resulting proficiency coefficient *r*. As shown in Figure 45, all 15 combinations of these parameters are unique. Furthermore, *r* values are informative as to the correctness of the immediately preceding encounters.

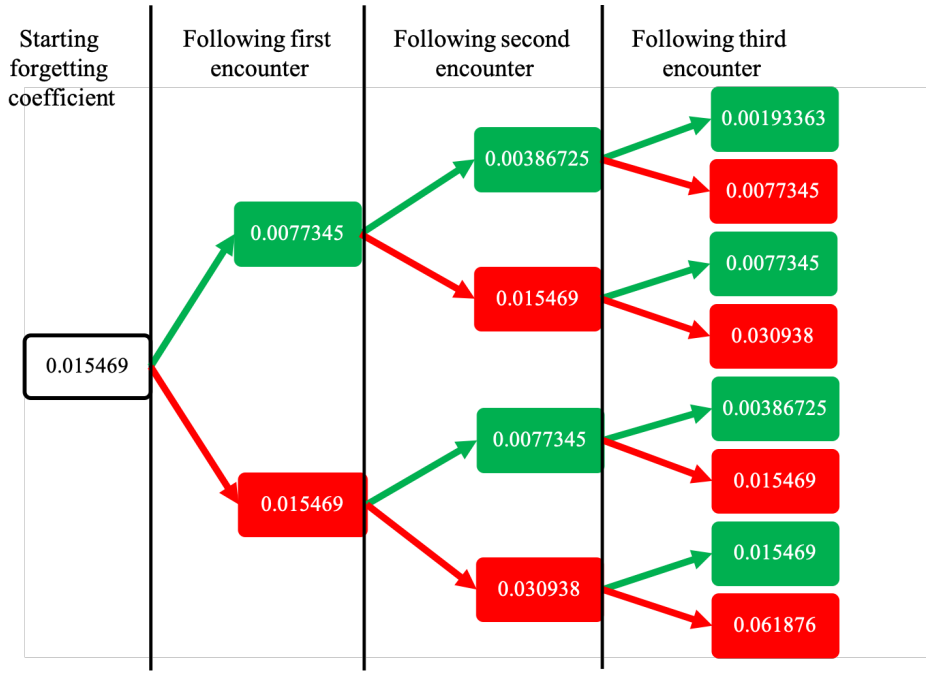

Figure 45: The development of the forgetting coefficient r during 3 consecutive question answer attempts as a function of answer correctness.

Figure 46 shows these relationships applied to the collected data. Seventy-six per-cent of questions were answered correctly upon a first encounter. These questions were answered correctly also upon 98% of second encounters and upon 92% of third encounters.

A learning effect was noted among learners responsible for the initial 24% incorrect responses. When encountered again, 82% of these questions were answered correctly and this learning effect was fully (100%) retained upon the third encounter. The 18% failed responses upon a second encounter may have originated from users not interested in learning, as none of them made a third answer attempt.

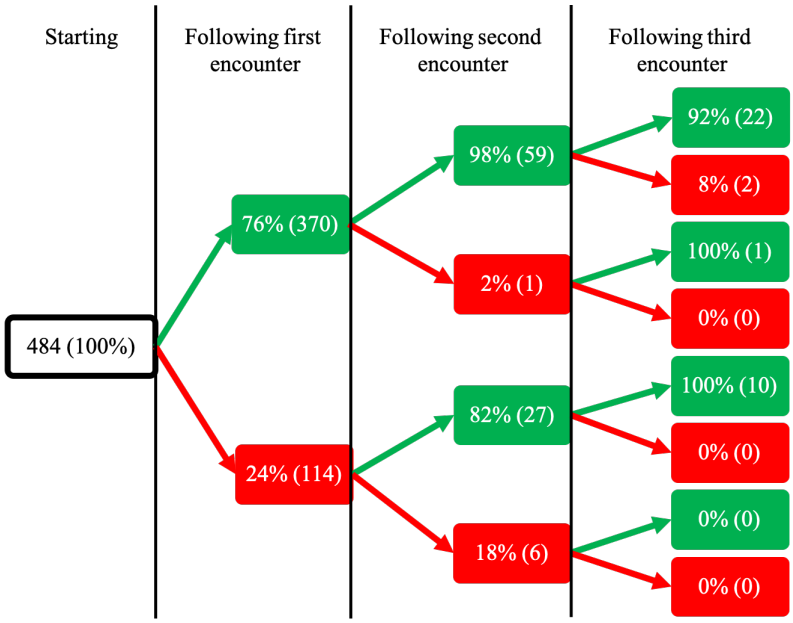

Figure 46: The learning effect driven by the repetition of PharmaFrog questions.

Were LUs used?

The KEs analyzed were all accessed through the TEACH ME learning mode. Altogether there were 130 events of reading KEs, which originated from a total of 22 LUs (Figure 47). On average, the time spent reading a KE was 47 seconds. This considerable time did not seem to translate into increased correctness of question responses. Indeed, the percentage of these questions answered correctly (68%) was almost identical to that of questions answered correctly through QUIZ ME mode (69%). A two-sample proportion z-test revealed no statistically significant difference between these two percentages. This suggests that users did not read the KE content, but rather explored the LU architecture. This is consistent with the fact that 25% of KEs were read within 6 and less seconds, a time much too short to comprehend their content. Every-second KE reading was completed (or terminated) within 18 seconds.

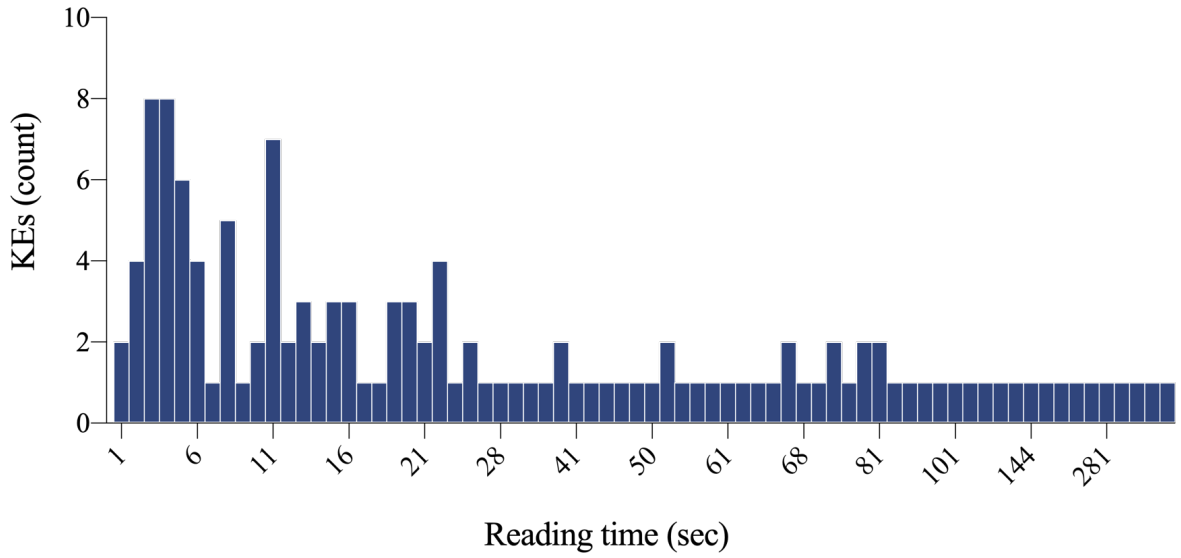

Figure 47: Number of KEs read in a given period of time.

A LU is considered complete when all its KEs have been read and all questions answered. Most drugs LUs have 4 KEs and Indications have 10 KEs in total. The level of completing the LUs was low. A majority of the learners quit after reading the first KE (Table 12, indicated by zeros and red color). Only three Drugs (acetylsalicylic (38%), alteplase (25%), amlodipine (50%)) and two Indications (atrial fibrillation (20%) and hypertension (75%)) LUs were read until the end by the percentages of all attempts given in parentheses.

Were KEs accessed from questions?

Further information can be accessed after answering a question through the book icons provided for each answer choice and additionally through a 'More information' button for questions accessed through QUIZ ME and REFRESHERs. There were 73 events in which further information was accessed, accounting for only 8 % of all the 883 question attempts. 94 % of the events were from questions accessed through QUIZ ME, 2 % through REFRESHERs and 4% through TEACH ME. Unfortunately, it was not possible to trace if these events were related to answering the question wrongly or not.

		Reading events per KE (count)										Level of completeness of reading LU (%)									
		KE_1	KE_2	KE_3	KE_4	KE_5	KE_6	KE_7	KE_8	KE_9	KE_{10}	KE_1	KE_2	KE_3	KE_4	KE_5	KE_6	KE_7	KE_8	KE_9	KE_{10}
DRUGS	acetylsalicylic acid	8	2	2	3							100	25	25	38						
	alteplase	4	1	1	1							100	25	25	25						
	amiodarone	3	1	1	1	1	0	0	0	0	0	100	33	33	33	33	0	0	0	0	0
	amlodipine	4	2	2	2							100	50	50	50						
	apixaban	1	0	0	0							100	0	0	0						
	benznidazole	2	0	0	0	0	0					100	0	0	0	0	0				
	bisoprolol	2	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
	clopidogrel	2	0	0	0							100	0	0	0						
	digoxin	3	2	0	0	0	0	0	0			100	67	0	0	0	0	0	0		
	furosemide	3	1	0	0							100	33	0	0						
	insulin, normal	2	0	0	0							100	0	0	0						
	metformin	1	0	0	0							100	0	0	0						
	methyldopa	1	0	0	0							100	0	0	0						
INDICATIONS	atrial fibrillation	5	1	1	1	1	1	1	1	1	1	100	20	20	20	20	20	20	20	20	20
	chagas disease	3										100	0	0	0	0	0	0	0	0	0
	coronary syndromes	3	3	2								100	100	67	0	0	0	0	0	0	0
	diabetes mellitus	1	1	1	1							100	100	100	100	0	0	0	0	0	0
	heart failure	1	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
	hypertension	4	3	3	3	3	3	3	3	3	3	100	75	75	75	75	75	75	75	75	75
	venous thromboembolism	1	1	1								100	100	100	0	0	0	0	0	0	0

Table 12: Reading events per KE.

DISCUSSION

Due to the pronounced multidisciplinary character of this thesis it is considered prudent to begin with a brief, chronological summary of the project stages, achievements, and findings. This will be followed by the discussion of the learning framework and of the resulting learning experience with the app.

Introductory summary

The development of the PharmaFrog app consisted of two phases:

Phase I: Implementation of the information lookup functionality SHOW ME. The information scope covered indications and drugs, with many additional knowledge subcategories ranging from the physiology of drug targets to common clinical situations. This functionality was deployed as the app version 1.0 in November 2017, covering 7 indications and 31 drugs. It had 1190 installations from 99 countries within a period of 6 months. The user interaction behavior guided the app development in the second phase.

Phase II: Implementation of interactive learning functionalities. This included first of all the selection of learning activities and thereby the development of a learning framework for PharmaFrog. To this end, the most important LTs and leading learning apps were analyzed for learning-promoting activities. A number of these activities were then selected, supplemented by activities identified by students and experts, and implemented in the app. The learning elements of PharmaFrog are derived mostly from Behaviorism, Cognitivism and Constructivism. They include chunking, personalization, interactivity, reinforcement, repetitions, case scenarios, adaptive learning, summary, associations, linking concepts, cues, discrimination, feedback and sequenced learning. Altogether, they form the basis of the four learning modes of PharmaFrog 2.0 SHOW ME, TEACH ME, QUIZ ME and REFRESHERS. All modes but SHOW ME share multiple-choice questions generated automatically by the templates connecting various KEs. These questions are deployed in sets of 10 via QUIZ ME and individually as REFRESHERS. Questions interspaced with the related KEs form LUs accessible via TEACH ME. The app was deployed in December 2019 as version 2.0 and observed for a period of two months. The app had 1313 visits from 28 countries and received a positive user evaluation despite the limited content scope. It was rated useful by 77% of the survey participants. One of the interviewed participants referred to it as a ‘pocket book’. App usage behavior provided a preliminary, but robust evidence for a learning effect.

PharmaFrog learning framework

This section of the Discussion deals with the PharmaFrog learning framework, i.e. with the key activities that enable and facilitate learning using the app. They were identified and compiled from analyzing selected LTs, mapping learning activities of leading apps to LTs, and modified by user

preferences and expert suggestions identified in preceding and subsequent PharmaFrog mockup evaluations. The resulting learning framework of PharmaFrog has at its core learning activities derived from Behaviorism, Cognitivism and Constructivism. They provide the learner with an interactive, personalized and adaptive learning experience. Combining elements from various LTs has been used and is recommended for eML, since no specific LT has been developed for eML (MacCallum and Parsons, 2016).

Selection of learning activities

The learning activities to be implemented in PharmaFrog were identified via three complementary approaches.

Top-down-up approach

LTs recommended for eML by MacCallum et al. (2016) and Leńko-Szymańska and Boulton (2015), supplemented with several other LTs, were dissected into learning elements. For better handling, learning elements were then grouped in 17 higher-order categories termed **learning activities**. Hence the name of this approach: top-down accounts for the dissection of LTs into learning elements; down-up for the grouping of elements into activities.

Twelve (80%) activities were shared by two or more LTs. All 17 activities were contained in at least one of the three classical LTs i.e. Behaviorism, Cognitivism, and Constructivism. Therefore, all subsequent work on the framework was referred to these three classical LTs. Taken together, the LTs analysis provided, first of all, an overview of the various concepts explaining how the learning process takes place. Secondly, it resulted in a manageable list of 17 learning activities to be used in the subsequent bottom-up approach.

Bottom-up approach

Technically, this step can be compared with the down-up part of the LT analysis. In other words, learning elements were combined into learning activities. The key difference is that learning elements were derived not from LT dissection, but from a set of existing and popular learning apps. The analysis was expanded from medicine onto other subjects and formats, including languages, mathematics, and MOOCs. Language apps were considered, because they had made the most progress in eML (MacCallum and Parsons, 2016). In consequence, they were expected to contain the most advanced learning elements, which could be used for informed decision in designing learning activities for other subjects such as pharmacology. MOOCs are open access courses typically created by universities and accessible by learners around the globe free of charge via internet-enabled electronic devices (Swinnerton et al., 2017). Some researchers have indicated MOOCs to be a particularly effective global means for delivering free medical education electronically (Robinson, 2018).

The most prominent learning activities in apps were personalization, illustrations, reinforcement and interactivity.[23] Although most apps did not disclose information about the underlying learning frameworks, it was obvious that all analyzed apps, consciously or not, applied elements of LTs. This is demonstrated by the matching of app-derived activities to the LT-derived activities in Table 4. Some activities went beyond the list derived from LT analysis. They included placement tests, external links, and personalization. Unsurprisingly, these activities are strongly IT technology-driven. In other words, they were developed following the completion of the three classical LTs they were mapped to.

Feedback approach

The LT and app analysis were combined with the results of the preceding PharmaFrog concept research (Frensch, 2019; Tibyampansha, 2015; Westervelt Natalia, 2015). The resulting 14 learning-promoting activities were strongly shaped by the detailed description of the app content and scope by Frensch (2019). Cognitivism was the most prominent LT, accounting for 10 out of 14 activities. The IT-driven adaptive learning and personalization were beyond the scope of Behaviorism, Cognitivism, and Constructivism. It is not clear which theories can best explain adaptation and personalization. Nandigam et al. (2014) suggest personalization to have originated from the theory of multiple intelligences and associate its elements with constructivism LT. A theory of adaptive e-learning is still under development (Šarmanová and Kostolányová, 2015).

Implementation

Chunking

Chunking is a key element of Cognitivism LT. As suggested by its name, chunking means breaking long strings of information into small manageable units, which reduces the cognitive load. This makes the information easier to process and improves the learning outcome (Thalmann et al., 2019).

Chunking is at the core of PharmaFrog. Originally, it was deployed to reduce the complexity of drug prescribing information. Indeed, with some care and attention, each piece of data can be clearly assigned to one and only one of the categories and subcategories of PharmaFrog, beginning with the basic information unit KE. In addition to reducing complexity, chunking minimizes redundancies and adapts content to the smartphone format. Chunking is also expected to help users to finish rather than give up learning a given Drug or Indication through providing break opportunities. Such breaks reduce the eye strain resulting from the small screen size.

The chunking-based, strictly categorized app architecture enables most PharmaFrog learning activities described above and discussed in the following. Briefly summarized, the semantic

[23] The LT-derived activities chunking, critical thinking and discrimination were not assessed in apps, as this would have required specialized knowledge of the topic covered by each app.

connections among the various knowledge chunks make possible the automated questions and thereby LUs, quizzes, and refreshers.

Associations

All knowledge categories and subcategories resulting from chunking are labeled with icons in one of four different colors. The icons are meant to help learners quickly identify the information category, which is consistent with Cognitivism. For example, each drug is preceded with a pill icon. The colors were taken from the traffic light code and expanded. Orange is reserved for Indications, as it conveys a sense of danger and urgency. Red is used to alert the learner to the need to postpone or even stop pharmacotherapy. This is the case when considering drug warnings, precautions and contraindications summarized in the "To consider" category, and when encountering ADRs. Green indicates proceeding with normal pharmacotherapy deployment. The additional and traffic-neutral blue is used to mark the physiological basis of drug action and the Library articles. Besides Cognitivism, icon- and color-based associations subscribe to Behaviorism (Savalia et al., 2016). Indeed, learners gradually get to identify knowledge using symbols, forming habits requiring less attention.

Linking

PharmaFrog employs various predetermined links to create many, partly innovative categories and subcategories, which are presented as lists throughout the app. This organizes the information in a hierarchical manner, in agreement with Cognitivism and Constructivism. The predetermined links constitute the basis for the various sequencing-based knowledge presentations, including LUs.

In addition, PharmaFrog features Wikipedia-like hyperlinks, which can be manually added to the text of KEs. These hyperlinks serve two purposes. Firstly, they reduce as much as possible content redundancies. Thus, concepts that are already presented in other parts of the app are not described again, but hyperlinked to the appropriate KE. This helps to reduce the content volume and improves the learning experience. Secondly, in-text hyperlinks create and reinforce connections between KEs.

The originally planned automatic hyperlinking turned out to be impractical. The multitude of hyperlinks reduced the reading experience. Currently, hyperlinks are inserted manually and sparingly, i.e. only upon the first occurrence of the KE to be referred to in a given KE.

Sequencing

Broadly speaking, sequencing is the ability to perceive, represent and execute a set of actions that follow a particular order. It follows that sequencing underlies many human activities beyond learning, including planning and problem solving (Savalia et al., 2016). In PharmaFrog, sequencing is enabled generally by chunking and linking, and facilitated by icon- and color-based associations. Specifically, sequencing is used in PharmaFrog in:

- **SHOW ME and TEACH ME**: The KEs of these key learning modes of PharmaFrog are organized in an order of causation (Drugs and Indications) and/or chronology (Indications). This makes the related KEs easy to link into sequences, which is consistent with Cognitivism.

- **Diagrams**: Cognitivism emphasizes the importance of a hierarchical knowledge organization. As discussed above, hierarchies are deployed throughout PharmaFrog through linking. However, some of them constitute knowledge sequences. An easily understandable example is the sequence Drug -> MM -> CM -> CM-G, displayed in various contexts throughout the app:

    - in Drug cards
    - in Diagrams summarizing the therapy of a given Indication
    - in the Therapy goals section of Indication cards
    - in the Summary card of Drug LUs.

In addition to Cognitivism, sequencing derives from Behaviorism (Savalia et al., 2016). Indeed, as learners gradually get accustomed to the KE sequences and to their graphical depictions, following them, for example in the LUs context, becomes a habit and requires less attention.

Cues

Cues are a special type of sequencing-supporting functionality that is deployed in LUs. Cues are short phrases preceding KEs and generated automatically using connections underlying LUs. They summarize the material just covered and connect it with the upcoming one. The resulting narrative strives to help connect KEs into a story, thus facilitating understanding and reducing LU terminations. Further, cues capture the learner's attention to the essence of the connected KEs. Cues are elements of behavioral and cognitive learning. As revealed by the app analysis, cues are frequently deployed in medicine to emphasize the most critical information. Otherwise, they have been shown to help children with learning difficulties (Costa et al., 2019).

Summaries

In all four learning modes, PharmaFrog deploys a cognitive technique of summarizing (Yilmaz, 2011). Summaries help learners to get a quick overview of what has been covered and learned. They are widely used in eML. For example, they were found in all app categories analyzed for the present project.

In PharmaFrog, summaries are all data presentations discussed above in the subsection Sequencing. In addition, the 'In a nutshell' KE at the top of Indication cards provides a brief summary of the essence, signs, and treatment of the indication to be studied. This summary is meant to lower the threshold for starting learning Indications. To this end, 'In a nutshell' is written using short sentences in a plain, easily understandable language.

Personalization

Learners are different, with no fixed learning path appropriate for all of them (Khamis, 2015). Personalization features help the learner find and filter the information in a way that fits their needs and interests (Pavlov and Paneva, 2006). In consequence, personalization gives the learner a sense of ownership and control over learning. In PharmaFrog, personalization is achieved via the following features:

- Learners can choose among four learning modes (TEACH ME, QUIZ ME, SHOW ME and REFRESHERs).

- The offline availability makes the app available to learners all the time. Learners have control of their learning pace. They are free to interrupt and later continue LUs and quizzes, or to terminate them altogether.

- Learners decide what to study and may find the information in several different ways. In the SHOW ME mode, learners can easily switch from one piece of information to another using in-text links and other navigation functions. In interactive modes (TEACH ME, QUIZ ME and REFRESHERs), the learner selects the drugs and indications of interest. The search function makes it easier to arrive at specific pieces of information. Throughout the app, navigation assures finding the desired content with a minimal number of clicks.

Interactive learning

Interactivity is a key element of Cognitivism, with the main focus on providing active learner experience. In PharmaFrog, learners actively engage with the app through questions. Through appropriate navigation elements such as book icons and the “More information” button, learners can immediately access the KE the question just answered is derived from.

The questions are generated automatically. Programming and testing them constituted a substantial portion of the overall PharmaFrog development effort. This was caused by the aforementioned, drug- or indication-driven needs to exclude either individual answer options, or even entire questions, from certain LUs.

The questions can be accessed via LUs, quizzes and refreshers. The great potential of questions deployed in these learning modes lies in the improvement of both learning experience and of learning outcome. Hsennig et al. (2019) demonstrated that quizzes improved students’ performance and satisfaction in the closely related field of clinical pharmacokinetics.

Case scenarios

Case scenarios are deployed as the first question of Indication LUs. The main motivation for introducing this activity was to expose the learners to conditions maximally similar to real-life contacts with patients. This has been shown to be beneficial for future clinical practice (McLean, 2016; Sowden et al., 2017). Another motivation was to introduce an element of diagnosis based on

the presented patient characteristics. All Indications have one case scenario question. The case scenarios presented in a way that the learner is able to identify the disease the patient is suffering from, using signs and symptoms presented in the preceding KE "In a nutshell".

Use of real-life situations in teaching is characteristic for Cognitivism and Constructivism. In medical education, they are deployed as case scenario vignettes, simulations and in problem-based learning formats (Karimi Moonaghi and Lotfi fatemi, 2018; McLean, 2016; Ryall et al., 2016). The app analysis presented in this thesis revealed that medical apps tended to use more case scenarios than other apps. Use of case scenarios has a potential of improving the learners' knowledge, confidence, and satisfaction (McCormick et al., 2010; McLean, 2016).

Discrimination

Discrimination is an important parameter in question deployment. Incorrect answer choices must be sufficiently far from the correct answer choice. For automatic questions, discrimination is largely assured by the mutually exclusive and non-redundant content structure enabled by chunking.

Feedback to questions

Every answered question is accompanied in PharmaFrog by an immediate, negative and/or positive feedback. Feedback is an element of both Behaviorism and Cognitivism LTs (Ellis, 2009). For example, the learner's awareness of the wrong or correct answer constitutes a cognitive effect (Rassaei, 2013). The feedback affirms that a learner gets the correct answer to the question. This is viewed as a means to ensure accuracy and foster learner motivation. Feedback has been successfully used in language apps (Ellis, 2009; Naeimi et al., 2018).

Adaptive learning

Pavlov et al. (2006) define adaptive learning as 'the capability to modify any individual student's learning experience as a function of information obtained through their performance on situated tasks or assessments.' The interactive learning modes of PharmaFrog adapt the learning scope and intensity both to learner's performance and to content difficulty. Easier questions and KEs require less repetitions, difficult ones require more. The same is true for learners capable of better memorization and retention of knowledge. This adjustment is assured by an algorithm monitoring the learner's proficiency in the knowledge covered by the app. Taken together, the algorithm adapts the intensity of learning to the individual knowledge retrieval performance.

Spaced repetition

Whenever needed, a learner should be able to retrieve from memory and apply the information self-defined as important. However, this is not always the case as learners forget a large portion of knowledge with time if no efforts are made to retain it (Murre and Dros, 2015). Hermann

Ebbinghaus (1885) demonstrated with several memorization experiments on himself, that it was possible to noticeably improve knowledge retention by revisiting the content periodically.

When and how often should knowledge be revisited? Spaced repetition is a "learning technique for efficient memorization & practice of skills" (Gwern, 2009).[24] It requires the learner to revisit the learning content at increasing time intervals ultimately culminating in long-term retention of memory (Gwern, 2009; Karpicke and Roediger III, 2007; Tabibian et al., 2017). Spaced repetition was originally implemented in Pimsleur's language courses (Pimsleur, 1967) and thereafter in physical flashcards. Of late, it has become increasingly popular in websites and apps such as Rosetta Stone, Mnemosyne, Synap, SuperMemo, and Duolingo (Appendix I).

PharmaFrog utilizes a modified Leitner System (Leitner, 1972), which amounts to a **retrieval at doubling or halving intervals**. The spacing intervals double for questions answered correctly. Items forgotten since the last practice are assigned a previous (i.e. twice-shorter shorter) spacing interval until the next check. The controlling *r* value is affected only by question answers and neither through SHOW ME nor by reading the information linked via question options. This restriction reflects the aforementioned uncertainty regarding the time and intensity of reading.

Questions derived from KEs with the least proficiency within the selected learning scope are triggered first in REFRESHER and QUIZ ME modes. Likewise, LUs with least proficiencies are presented first in the TEACH ME mode. In this way, the learning is adopted to the learner's needs and abilities (Khamis, 2015; Pavlov and Paneva, 2006). Simultaneously, this mechanism facilitates adopting learning to the KEs level of difficulty. Unlike in the original Leitner System, the duration between the repetitions is better adapted to learner's needs and preferences. For example, the REFRESHERs trigger only as set by the learner, and other learning modes can be accessed whenever convenient.

Reinforcement

Reinforcement is rooted in behaviorism (Pavlov, 2010; Skinner, 2011) and refers to the introduction of a desirable stimulus after a behavior. The desirable stimulus reinforces the behavior, making it more likely to reoccur. Reinforcements were used across all app types analyzed. In PharmaFrog, learners are rewarded positively for participation with proficiency for participating in all activities featured by the app. Rewards often elicit motivation for learning (Wittmann et al., 2011). Learners become proficient even when failing questions, because the automatic exposure to the correct answer constitutes a learning effect. The only penalty for wrong answers is the decay of the *r* coefficient, when failing to answer a question. However, the penalty, i.e. the halving of the time to the next deployment of the question just failed, is not communicated to the learner and may even go unnoticed.

[24] Spaced repetition should be differentiated from the short-term spaced learning, which takes place on a much shorter time scale. A learner is presented with a KE three times, separated by 10-20 minutes destructor breaks. The breaks involve unrelated activities such as sports or games (Kelley, 2007; Fields, 2005).

Learning with PharmaFrog

Who benefits from PharmaFrog?

Most generally, PharmaFrog is supposed to benefit patients. This is achieved through targeting students and junior health professionals of medicine, nursing and pharmacy. PharmaFrog makes the complex interdisciplinary topic of pharmacotherapy more accessible and understandable, by presenting it in a structured and logical way. Simply put, the app emphasizes **why** a given treatment is offered to a patient, as opposed to the customary **what** treatment is offered.

To this end, PharmaFrog employs causal connections between its KEs. This causal thinking is promoted particularly through LUs, which constitute the most original part of the app. The originality starts with the introduction of interactivity into a complex, multidisciplinary body of KEs, which is supposed to promote self-learning. Furthermore, LUs make users develop a way of thinking conductive to rational, error-free prescribing. To this end, they are made familiar first with the pathophysiology of a given disease, followed by the identification of one or more treatment goals. This, in turn, determines the selection of CMs that need drug modulation. The activities of CMs depend on the action of one or more MMs accessible to drugs. Through alternation of KEs with questions users gradually develop a habit to reflect and justify their prescribing actions, instead of the customary learning by heart. The LU-mediated promotion of reflection and causal thinking is more important than learning the individual drugs and dosages. Indeed, PharmaFrog is designed for learning purposes only, with users advised to follow their country- and hospital-specific guidelines, when prescribing drugs to patients.

PharmaFrog, especially its LUs, may be particularly useful to students in resource-limited settings. Healthcare schools in such settings are overwhelmed with recent increases in student enrollments that are not matched by qualified faculty members and access to up-to-date learning content (Agyepong et al., 2017; Mullan et al., 2011). Despite many schools adopting e-learning to cover for faculty shortage (Frehywot et al., 2013; Kelly et al., 2019; Lisasi et al., 2014; Vovides et al., 2014), they still face the problem of poor instructional design. PharmaFrog addresses those shortcomings in the scope relevant to pharmacotherapy. It substitutes for pharmacology faculty and offers interactive, self-learning resources addressing the entire range of relevant knowledge, from physiology to clinical situations. The offline availability makes the information available to the users wherever and whenever they wish to access it. Strict categorization of data, primarily necessitated by the LU architecture, is expected to make the app easy to understand and use. Although fore mostly developed as a self-learning tool, the app could be easily adapted in resource-limited settings to determine the prescribing curriculum. This could include both the formative and summative assessment of prescribing-related knowledge.

What was taught?

PharmaFrog 2.0 tested in early 2020 featured 7 cardiovascular indications and 34 drugs, corresponding to some 10% of the envisioned app scope. The cardiovascular diseases were selected deliberately for the prototype phase of the project, due to their interconnectedness and pathophysiological complexity. For example, hypertension predisposes to coronary syndromes. In turn, both hypertension and coronary syndromes may result in heart failure, especially when present in one and the same patient. Further, some cardiovascular drugs affect the activity of multiple MMs, and most of multiple CMs. The assumption was that once these complexities have been accommodated, the resulting app architecture would be able to deal with any future content. Additionally, hypertension and its consequences account for 15 percent of the global disease burden (Roser and Ritchie, 2016).

Unsurprisingly, many respondents considered this disease and drug spectrum insufficient to meet their needs. This is currently being addressed as described in the section Next steps. Some users suggested a full consideration of country-specific Standard Treatment Guidelines, which - at least theoretically - form the basis of national curricula for pharmacology and pharmacotherapy. Accommodating this wish is at present impossible, as Standard Treatment Guidelines vary enormously even among countries with similar economies and disease burdens. Furthermore, some drugs are approved for country-specific disease spectra and dosage regimens. Lastly, some national guidelines are simply outdated. The PharmaFrog project strives to help all resource-limited countries. The meanagable compromise is to follow for the time being the WHO-recommended (WHO, 2019) drug list and expand it as necessary. Eighty per-cent of the drugs included in the tested version are WHO Essential Drugs.

Learn as you wish

Learning modes

Every student learns differently, regarding the preferred format, speed, and the overall style (Truong, 2016). At a first glance, PharmaFrog caters mostly to the reading learning style. Upon a closer look, it appeals also to the predominant, visual style. Indeed, several cards include diagrammatic representations of PharmaFrog KEs and/or cards. Besides summarizing content, these cards emphasize also the relatedness among various elements as well as convey a sense of hierarchy. For example, a drug invariably first modulates the activity of its MM, and only secondarily of one or more CMs. Likewise, drugs are deployed to reach specific therapy goals, which is accomplished by modulating appropriate MMs and CMs. These relationships would be much more difficult to comprehend using only text-based descriptions.

The app accommodates the various learning needs by featuring four learning modes: TEACH ME, QUIZ ME, SHOW ME and REFRESHERS:

- The SHOW ME learning mode serves users who prefer passive, reading-based learning and those searching for a specific information piece. The information in this mode is grouped in categories and presented in a systematic and logical manner. The interrelated pieces of information are further interlinked via in-text hyperlinks, enabling the learner to associate the information and to move rapidly from one piece of information to another.

- The TEACH ME learning mode caters for learners who are exposed to the material for the first time, especially to those who need to systematically immerse themselves in a certain topic for a full understanding. To provide an overall narrative, every KE is introduced with a cue referring to and thereby connecting with the immediately preceding KE. Each KE is followed by one or more questions. The questions verify the understanding of the material, but also provide an interactive alternation to the reading routine.

- The QUIZ ME and REFRESHERS primarily address learners who need to review or retain material already learned. The learners get immediate feedback regarding the correctness of the response. If wished, they may consult the pertinent knowledge, which is immediately accessible via dedicated navigation elements such as the book icons of the individual answer options. Each icon opens the KE the associated answer option has been generated from.

At any time, learners can switch from one learning mode to another. This is enabled by all four activities covering the same content presented in different ways. What differentiates the modes as listed above, is the gradual transition from passive knowledge acquisition to interactive knowledge retrieval.

The preferred mode

Among the four learning modes of PharmaFrog 2.0, SHOW ME was the most popular one, accounting for almost two-thirds of the traffic originating from the home screen. To some extent, this preference may have been brought about by the familiarity of users with this learning mode. Indeed, PharmaFrog 1.0, which consisted exclusively of SHOW ME elements, had been introduced to the same target audience two years earlier. An alternative explanation is that SHOW ME leads to a comprehensive overview of knowledge categories (e.g. Drugs, Indications, ADRs) that users easily recognize. Yet another, trivial but quite likely explanation is the placement of SHOW ME at the top of the Home screen. In support of this possibility, also the most frequently accessed Drug and Indication cards were those[25] placed at the top of the respective A-Z list. Lastly, SHOW ME may have attracted more traffic due to its passive and thereby less intimidating label, compared to the more challenging TEACH ME and QUIZ ME names.

[25] Acetylsalicylic acid and atrial fibrillation

Similarly, multifarious may have been the reasons for the altogether limited, yet very different usage of the interactive learning modes TEACH ME and QUIZ ME.[26] These two modes accounted for only 20% of the traffic originating from the Home screen. The observed dominance of question use via QUIZ ME, as compared to TEACH ME, may have been caused by the familiarity of users with the quiz format from other learning apps and from school experience.

The most innovative interactive mode, i.e. TEACH ME, attracted much less interest than anticipated, with many LUs terminated after opening the first KE. This result could reflect a failure to engage users, but this conclusion is incompatible with the overwhelmingly positive assessment of the app concept by users. Admittedly, the assessment gathered from group discussions may have been skewed towards more favorable comments due to the on-site presence of a developer of PharmaFrog. However, PharmaFrog was judged very favorably also in the fully anonymous surveys triggered by the app. What was the reason for the limited interest in TEACH ME despite an overwhelmingly good evaluation?

This limited use of TEACH ME during the testing period can be best explained by the peculiarities of the testing cohort and of the testing time-point. Specialists, graduates and advanced students accounted for the overwhelming majority of the testing cohort. These testers had no need to learn the content presented in the app. Regarding the younger, i.e. less advanced testers such as MD2 students, they may have had the need to learn, as suggested by the considerable (24%) proportion of wrong answers in the entire cohort. However, the testing took place without any coordination with the curriculum being covered during the test. Taken together, the test was exploratory rather than driven by real learning, or at least lookup, needs. This conclusion is consistent with the rapid and thereby random selection of a majority of question options. It is also in agreement with the aforementioned preference of testers for categories and items located at the top of the pertinent screens and lists. A fuller evaluation will be possible once the app has been adopted and used by a larger number of users over a longer period of time. Ideally, the app should be deployed and evaluated as an auxiliary tool within a pharmacology or pharmacotherapy course.

Have users learned?

PharmaFrog is designed to help users not only learn, but also retain the learned material. To this end, PharmaFrog deploys the concept of dynamic proficiency, which is currently applied to Drugs and Indications. Proficiency is built up and maintained through answering multiple choice questions and through reading KEs these questions are derived from. The relative contributions of reading versus answering questions vary depending on the preferred learning mode.

The limited usage and the short sampling time preclude at present any firm conclusions about the app's effect on long-term proficiency. Nevertheless, a careful analysis of the data suggests a robust

[26] REFRESHERS are not included in the Home screen, but could be compared to TEACH ME and QUIZ ME by analyzing the usage of questions, which are deployed in all three modes. However, the use of REFRESHERS cannot be interpreted at this stage, as triggering them was plagued by technical problems.

learning effect, which is derived from the analysis of the testers who failed to answer questions upon a first encounter. When encountered for a second time by the same learners, 82% of these questions were answered correctly. This percentage reached 100 upon a third encounter. This impressive result awaits confirmation on a larger cohort of users.

IT structure and hosting

Due to the complexity and the number of parties involved, the development of PharmaFrog has been coordinated using the Agile project management model. Changes were made in the smallest possible increments with frequent and rapid feedback among pharmacology experts, testers, and app developers. Cloud hosting was chosen to minimize the management overhead.

Offline availability

The offline availability of PharmaFrog information was originally decided based on the peculiarities of Internet access in resource-limited areas. The app is intended to be of help in disadvantaged areas which are typically characterized by poor connectivity. The coverage has improved markedly in such areas since the inception of the project. However, it seems that the offline character of PharmaFrog is still an advantage, independently from the location of the user. Crucially, it enables a more reliable and faster app user experience, as can be confirmed by anyone accessing an online app, especially in a typical concrete-constructed hospital or school building. PharmaFrog users will be spared the frustrations of slow app performance in any area of poor internet connectivity.

Additionally, the costs of a frequent as-needed data download were considered a potential burden limiting the app adoption by students, the preeminent group of users. This problem has been solved by implementing periodic database downloads. Based on the Internet tariffs in Tanzania in early 2020, downloading the current PharmaFrog app database of approximately 5 Mb costs a student less than 0.5 US cents. The long-term cost effectiveness of this update method will depend on the size and frequency of database updates versus the app use by the users. For an occasional user, an as-needed data download could be more cost-effective. Conversely, frequent users could profit from the offline availability. This could change with the database having become bigger, which would automatically increase the number and thereby the frequency of content corrections. At that stage, database updates could be made less frequent and simultaneously more comprehensive.

IT platform choices

PharmaFrog is a typical academic project run by enthusiastic individuals rather than a constant budget. It is mostly developed by students who come for a short time, with numerous other obligations and unscheduled availability. Therefore, it was necessary to keep the IT structure as simple, flexible and outsourced as possible. To speed up the app development, the following principles were adopted:

- PharmaFrog hosts all its elements and services on Microsoft Azure. This minimizes the time for expanding and maintaining the IT infrastructure, leaving more time to focus on app development. This is also conducive to the collaborative nature of the project, with all IT elements accessible from any computer connected to the Internet.
- Adopt the mobile development framework 'React Native', which facilitates cross-platform development. In other words, PharmaFrog is simultaneously developed for both dominating smartphone platforms Android and iOS.
- Adopt Agile project management, with small, informal and frequent development steps based on feedback from testers, users, and developers.

The PharmaFrog app structure allows for versatile use. This is exemplified by the fact that new features that were not envisioned at the beginning of the project, were smoothly implemented as needed. For example, the question exclusion feature was implemented towards the project's end, after receiving expert feedback.

Speed is important for PharmaFrog as for any other app. In addition to offline availability, it is assured by most of the data processing being done by the API: this means that the app just displays the information. The only computations that take place on the app side are the proficiency calculations and - until recently - triggering Refreshers.

Limitations

App analysis: The app analysis for learning elements was limited to apps that were accessible free of charge. Therefore, some additional learning elements may be missing in the app analysis. Likewise, not all learning activities resulting from learning theories could be assessed in the apps.

PharmaFrog faults: The REFRESHERs scheduling and triggering were originally handled by the app. In case a triggered REFRESHER was skipped, there would be further Refreshers in the absence of TEACH ME or QUIZ ME activity. This could explain the low usage of REFRESHERs during the testing period. The REFRESHER scheduling and trigger mechanism has been revised. Refreshers are now scheduled by the app, but triggered by the API to ensure regularity.

Limited content scope: At the time of usage analysis, PharmaFrog contained information of only seven Indications and the drugs to treat them. This limited the onboarding in Tanzania, where the majority of app users came from, due to the strong focus on infectious and neonatal diseases.

Limited question variety: The same question types were used across all Drug and Indication LUs. Although the content of the questions slightly changed for each question, this uniformity may have created a sense of repetition and monotony.

Limited usage data: Due to the above limitations, the amount of usage data was too small for a robust analysis of the user behavior and of the learning effect. Some data was not recorded,

notably the time gap between question repetitions. In consequence, the analysis lacks the effect of the time lag on the learning effect.

Next steps

Not all ideas developed by experts and students could be implemented during the time available for this project. Even more ideas have resulted from the various tests and surveys described in the present thesis. The tasks are listed in the order of the importance perceived by the developers. Before implementation, this will be verified by users via the survey link in the app.

Expanding the content: considering the overwhelmingly positive and sometimes even enthusiastic evaluations, the limited content scope is currently the most important reason for the limited uptake and retention of the app. The next stage will cover the five diseases considered to be particularly important in sub-Saharan Africa: malaria, tuberculosis, HIV/AIDS, diarrea, and pneumonia.

Confirm the learning effect: A first evidence of a learning effect is presented in this thesis. A confirmation would have to include a higher number of users learning bigger proportions of KEs and answering more questions over a longer period of time. Eventually, this analysis could be expanded into more formal longitudinal evaluations involving benchmarking using standardized tests such as the aforementioned PSA.

Introduce customized questions: PharmaFrog contains a lot of important knowledge currently not assessable by automatic questions. For example, the enzyme ACE is presently assessed as the enzymatic target of ramipril affecting the activity of three physiological processes that control either the cardiac output or vessel patency. In contrast, the automatically generated questions assess neither the included knowledge on ACE tissue expression nor on its substrate spectrum. Similar limitations apply to virtually all KEs in the app. This will be addressed by providing an option of writing customized questions. This will also eliminate, or at least greatly reduce, the monotony resulting from the rigid sequence of questions and from the repetitive question prompts. This monotony was noted by one of the app evaluators from Tanzania.

Increase the pool of answer options in the app: To assure a sufficient app speed, the selection of a correct and of 3 incorrect options from the pool of all correct and incorrect options is currently done by the API, i.e. outside the app. The options selected are then transmitted to the app with the next database update. The app itself solely scrambles the sequence of the four transmitted options each time a given question is presented.

The other available options, whether correct or incorrect, get transmitted and displayed only with subsequent database updates. This is a limitation for questions with multiple correct options, especially in case of infrequent database updates. This limitation will be solved by transmitting to the app up to three correct and nine incorrect options. The selection of options for each deployment of a given question will be done by the app. This will assure a faster and thereby fuller presentation

of all correct options. The transmission of nine rather than three incorrect options will increase the number of combinations of 3 incorrect options from currently one to 84.

Refine reading-driven proficiency gain: As presented in Appendix H.

Enable resetting of proficiency: the proficiency of a KE will be reset to 0% following every major update of this KE. Simultaneously, the *r* value will be reset to the initial value of 0.015469.

Combined LU-Drug selection: The settings of TEACH ME and QUIZ ME could contain an additional option button "match selected drugs and indications". When activated, selecting a drug would automatically select indications this drug is indicated for. Conversely, choosing an indication would automatically select the pertinent drugs. Care must be taken to avoid self-amplification of this functionality to a point when all drugs and diseases have been selected.

Search: Once a card is opened from the search result window, the user is taken to the top of the card instead of the specific point in the article where the information searched for is contained. This costs users more time to locate the information and could be frustrating in the long run. This problem will be solved by highlighting the searched information in the card. Another problem to be addressed is the inflexibility of the search algorithm, which identifies terms exactly as typed in. A search term “hypertension drugs” will yield results only if these words are contained in the card content in this very order and without any interrupting words.

Perspective

The long-term potential of the PharmaFrog app is supported by the adaptation of its code to create two other apps currently in development:

- The Rheuma.VOR app is designed for general physicians and combines the SHOW Me part of PharmaFrog with a screening module, which is entirely new. The module consists of 17 questions to be answered by patients that interrogate present and past symptoms and the family history. The questions are designed to detect as early as possible, and differentiate among the three most common rheumatoid diseases, including rheumatoid arthritis. The Rheuma.VOR addresses the shortage of rheumatologists in Germany. The inclusion of SHOW ME is meant to increase the awareness of the biology of the three diseases, as well the understanding of the rapidly expanding pharmacotherapeutic options.

- UMmedis is an app designed to improve the usage of the internal treatment guidelines at the University Medical Center Mainz. Currently, these guidelines exist mostly as PDF files of very variable structure. The usage is limited by the poor wireless connectivity. The SHOW ME architecture will enable a much-needed standardization of the guidelines. Compared to PharmaFrog, the UMmedis app will contain some additional information categories related to the ordering and distribution of medications at the Center.

In relation to the original use, PharmaFrog could be improved using the tools of AI (artificial intelligence:

- **Revise the initial forgetting coefficient (*r*):** Currently, the app uses one-for-all starting r value, which changes for all users much in the same way. In reality, users master and retain knowledge at very individual rates. The various data collected by the app could be used to individualize *r* increments as well as the intensity and composition of the suggested interactions with the app.

- **Scheduling:** Learners, especially students, usually learn toward a specific examination goal. Based on an initial assessment and on the continuous subsequent data accumulation, the app could present and adapt an individual learning schedule ensuring reaching a sufficient knowledge level at a pre-specified time-point.

Lastly, PharmaFrog could benefit from automatic language translation. Currently the app content is written in English, which is not the first language for most targeted audiences. Users could profit from information presented in their native languages. The quality of automated translations is rapidly improving.

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APPENDICES

A. Learning theories and their elements

Activity	Learning elements	Behaviorism	Cognitivism	Constructivism	Situated learning	Experiential learning	Communities of practice	Sociocultural	Social cognitive theory	Social constructivism
Associations	Associations	yes								
	Metaphor		yes							
	Information Processing Model Explanations		yes							
Discrimination	Building fluency	yes								
	Analogies		yes							
	Discrimination (recalling facts)	yes								
	Matched non-examples		yes							
Case scenarios / real-life situations	case-based learning;			yes		yes				
	Real world examples		yes	yes		yes				
	Problem based learning					yes				
	Scenario based learning				yes					
	Authentic Learning			yes						
	Apprenticeship				yes	yes				
	Anchored Instruction									
	Roleplaying				yes				yes	
	Research Projects			yes						
	modeling			yes	yes					
	Discovery learning			yes						
	Role modeling and imitation								yes	
Chunking	Chunking Information		yes							
	Classifying or chunking information		yes							
	Schema Theory		yes							

Collaboration	Collaboration			yes	yes		yes	yes		
	Peer tutoring and learning									yes
	cooperative (work- or community-based) learning.					yes				
	Discussions	yes	yes				yes			
	Group activities			yes	yes		yes	yes		yes
	Group learning									yes
	Shared Storytelling							yes		
Feedback	Corrective feedback	yes	yes							
Illustrations/clarification	Dual-Coding Theory		yes							
	Illustrative examples	yes	yes							
	Imagery / providing pictures		yes							
	Taking photos,recording videos, notes and sound			yes						
	Demonstration		yes						yes	
	Simulations			yes						
	Generalization (defining and illustrating concepts)	yes								
cues	Instructional cues to elicit correct response	yes								
	Mnemonics		yes							
	Memory aids		yes							
	Outlining		yes							
Coaching	Coaching			yes	yes					
	Direct instruction	yes								
	Scaffolding			yes	yes			yes		yes
Interactivity	Questions	yes		yes						
	Interactivity		yes	yes						
	Active learning			yes						
Critical thinking	Discovery learning			yes						
	Reflection			yes	yes					
	Exploration				yes					
	Brainstorming			yes						

	Think-Aloud							yes		
	Transformative learning			yes						
	Inquiry-based learning					yes				
Reinforcement	penalty	yes								
	rewards	yes								
	Establishing Rules	yes								
	Reinforcement for correct responses	yes								
	Positive reinforcers (Points, Power-ups, Bonuses, Unlocks)	yes								
	Participation points (providing an incentive to participate)	yes								
	Social reinforcers (Status, Leaderboards)	yes								
	Negative reinforcers (Failure to beat high score, An increase in obstacles or opponents, A decline in health)	yes								
	Bonus points (providing an incentive to do more)	yes								
	Strategic use of reinforcement								yes	
Repetition	Repetition		yes							
	Repetitive practice		yes							
	Drill / Rote work	yes								
	Multiple practice				yes					
	Multiple opportunities/trials (drill and practice)	yes								
Schedule	Timing of feedback	yes								
Summaries	Summaries		yes							
Articulation	Meaningful learning		yes							
	Articulation				yes					
linking concepts	Linking Concepts (associate new content with something known)		yes							
	Concept Mapping		yes							
	Generative Learning		yes							
	Inquiry-based learning			yes						
	Elaboration Theory		yes							

	Gestalt Theory		yes							
	Links to prior knowledge		yes							
Sequencing	Providing structure/ follow order		yes							

Theory definitions

Behaviorism: Learning is defined as acquiring new behavior triggered by conditioning (Pavlov and Anrep, 2003; Skinner, 2011; Watson and Meazzini, 1977).
There are two types of conditioning;

- Classical conditioning: occurs when a natural reflex responds to a stimulus e.g. Pavlov's observation of dogs salivating on seeing food
- Operant conditioning: occurs when a response to a stimulus is reinforced with reward or punishment

(Driscoll and Carliner, 2005; James, 2012; Kay and Kibble, 2016; MacCallum and Parsons, 2016)

Cognitivism: Learning is attained through receiving, processing and storing, eventually leading to change in thoughts and perceptions. The key assumptions are (Bakan and Bakan, 2018):

- that the memory system is an active organized processor of information
- that prior knowledge plays an important role in learning

(Driscoll and Carliner, 2005; James, 2012; Kay and Kibble, 2016; MacCallum and Parsons, 2016)

Constructivism: A learner actively constructs new ideas/knowledge upon current and past knowledge or experience. Learning is based on how the individual interprets and creates the meaning of his or her experiences.
(Driscoll and Carliner, 2005; James, 2012; Kay and Kibble, 2016; MacCallum and Parsons, 2016)

Situated learning: Learning takes place through action in the same context in which knowledge is applied (Clancey, 1995; Suchman, 1987).Situated learning is guided by 4 principles:

1. Learning is grounded in actions of everyday situations
2. Knowledge is acquired situationally and transfers only to similar situations
3. Learning is a result of social environment interactions
4. Learning is not separate from the real world of action but exists in a robust, complex and social environment made up of actors, actions and situations.

(Chang et al., 2020; Herrington and Oliver, 1996; MacCallum and Parsons, 2016; McLellan, 1996)

Experiential learning: Knowledge is created through the transformation of experience. Learning by doing (Healey and Jenkins, 2000).

Communities of practice: "groups of people who share a concern or a passion for something they do and learn how to do it better as they interact regularly" (Wenger, 2011).

Sociocultural: Focuses on social interactions in the development of cognition. Learning takes place through social interactions (John-Steiner and Mahn, 1996).

Social cognitive theory: 'Learning is defined by observable increases, decreases, or maintenance of identified behaviors. Principles of behaviorism apply. However, they are expanded to include the role of observational and vicarious learning. In other words, a learner doesn't have to be directly reinforced in order to demonstrate a behavior' (Kay and Kibble, 2016).

Social constructivism: 'The learner uses the tools, signs, symbols, language, and more knowledgeable others to master the next level of understanding, knowledge, and/or skill. In some cases, learners can serve as the more knowledgeable others who can assist peers with learning goals'(Kay and Kibble, 2016).

B. Learning elements arising from eML apps

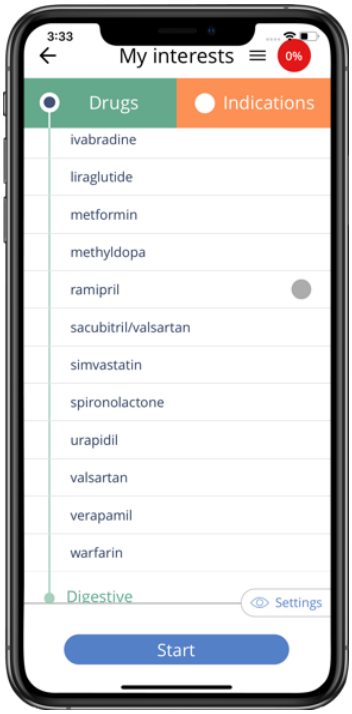
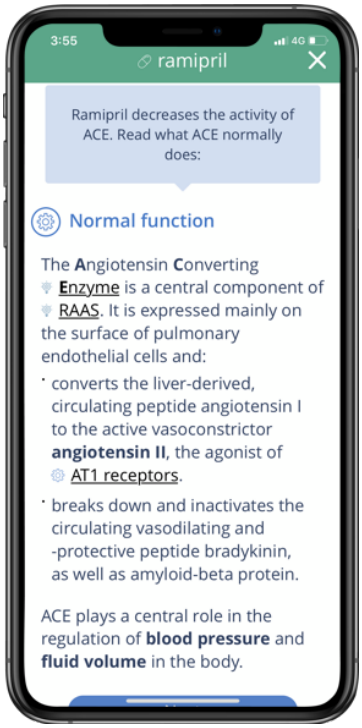
	APPS	Duolingo	HelloTalk	Mindsnacks	Busuu	Babbel	Memrise	Leaf	Lingua.ly	TripLingo	MosaLingua	HiNative	Rosetta Stone Language Learning	math42	sumaze	Khan Academy	Craftsy	Coursera	edx
Activities	**Learning elements**	**Language**												**Mathematics**		**General**		**MOOCs**	
Personalisation	Search function		1													1	1	1	1
	Note taking						1									1			
	Favourites/save /Flag													1			1		
	Study modes (e.g quiz , adoptive, game mode)																		
	Customise session to topics interested in													1			1		
	Set learning goals	1			1		1												
Collaboration/social	Discussion/clubs/language exchange partner	1			1		1											1	1
	coversation		1		1														
	Leader's board						1												
	Feedback about content/questions													1		1		1	
	Share information/question	1			1		1									1			
Content Formart	Images	1	1	1	1	1	1						1			1	1		
	Video		1				1	1								1	1	1	1
	Voice notes	1	1	1	1	1	1		1			1	1			1			
	Link to external sources e.g guidelines													1	1			1	1
	Live tutor												1						
	Lecture e.g PPT, PDF							1										1	1
	Charts											1							
	Decision support																		
	games			1											1				
	Case scenarios	1																	
Repeatition	Redo failed tasks/questions	1			1		1		1							1		1	1
	Loss of health overtime requiring to redo lesson	1							1										
	Spaced repeatation										1								
	Recommendation of topics to focus on																		

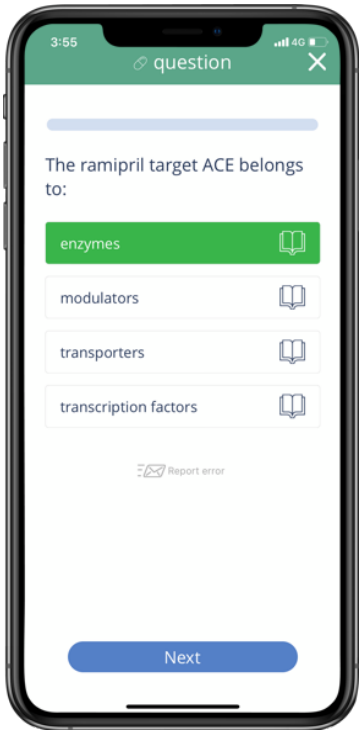
Learning sequence	There is order of following the modules	1			1	1	1											1	1
Assessment	Placement test	1			1	1	1												
	Quiz	1			1		1							1				1	
	Multiple choice questions				1	1	1							1				1	1
	Multiple select questions								1									1	1
	Matching items					1													
	Flash cards				1														
	Questions re connected to learning cards																	1	
	Additional information for every question prompt															1			
	Additional information for every answer choice																		
	Explanation for every answer choice													1				1	
	Highlight key words in a question																		
	exams																	1	
	Review of test/quiz/assessment with explanations				1	1	1		1					1				1	
Progress	Amount /volume of content covered e.g number of lessons	1				1	1		1				1	1		1		1	1
	Streak of learning days	1			1		1		1										
	Retention/mastery level	1			1				1				1						
	Score													1		1		1	1
	Timer												1						
	statistics													1				1	1
	Learning levels (beginner,intermediate, advanced)				1	1											1		1
Punishment	Completing a module unlocks next module	1			1	1			1										
	Loss of health	1																	
	negative score for wrong choice made																		
Rewards	Power ups/health/gems	1			1		1		1							1			
	Additional quest/challenge			1															
	certificates																	1	
	Credit especially in CME																		
Reminders	Scheduled reminders to continue lesson	1			1	1													
cues	Hint of what will be covered in a lesson	1			1	1	1		1									1	
Scheduled	Timed (Duration to take the course)																	1	1

	APPS	Daily rounds for Doctors	Prognosis	Figure 1	UBC Med Formulary	Brain scape	Johns Hopkins Guide	Pedi Anesth	Guideline ap	ACC 16	Pediatric Nursing quiz	Pediatric Nursing Practice Exam	Duke CPR	Brain HQ	Medcsape CME & Education	Resuscitation	iResus	XebraED	NICU flash	Pathophysiology Flash cards	USMLE step 1 Mastery	USMLE step 1	CPPE	meducation	AMBOSS	Flexkon
Activities	**Learning elements**	**Medical**																								
Personalisation	Search function	1			1																				1	1
	Note taking							1		1	1															1
	Favourites/save /Flag	1		1			1		1	1	1				1			1	1		1	1		1	1	1
	Study modes (e.g quiz , adoptive, game mode)																			1						
	Customise session to topics interested in																								1	
	Set learning goals																									
Collaboration/social	Discussion/clubs/language exchange partner	1		1	1					1														1		
	coversation																									
	Leader's board																					1				
	Feedback about content/questions			1		1																				1
	Share information/question		1		1					1											1					1
Content Formart	Images	1	1	1	1												1					1			1	1
	Video												1	1	1								1	1	1	
	Voice notes	1											1												1	
	Link to external sources e.g guidelines						1	1	1	1				1	1			1	1							1
	Live tutor																									
	Lecture e.g PPT, PDF				1																					
	Charts																	1								
	Decision support																		1							
	games																									
	Case scenarios	1	1	1							1	1			1	1		1	1	1	1				1	
Repeatition	Redo failed tasks/questions																					1				
	Loss of health overtime requiring to redo lesson					1																				
	Spaced repeatation																									
	Recommendation of topics to focus on																									1
Learning sequence	There is order of following the modules																									
Assessment	Placement test																									

	Quiz				1						1	1								1	1		1				
	Multiple choice questions	1									1	1			1						1		1	1	1		
	Multiple select questions		1																								
	Matching items																										
	Flash cards				1	1													1	1		1					
	Questions re connected to learning cards																										1
	Additional information for every question prompt										1										1		1		1		
	Additional information for every answer choice																								1		
	Explanation for every answer choice																										
	Highlight key words in a question																								1		
	exams																										
	Review of test/quiz/assessment with explanations		1								1	1			1			1			1						
Progress	Amount /volume of content covered e.g number of lessons	1	1			1										1					1	1			1		
	Streak of learning days													1							1						
	Retention/mastery level	1				1																1			1		
	Score										1	1			1					1	1		1		1		
	Timer										1														1		
	statistics			1																					1		
	Learning levels (beginner,intermediate, advanced)													1													
Punishment	Completing a module unlocks next module																										
	Loss of health																										
	negative score for wrong choice made																								1		
Rewards	Power ups/health/gems																										
	Additional quest/challenge																										
	certificates																										
	Credit especially in CME														1												
Reminders	Scheduled reminders to continue lesson									1											1						
cues	Hint of what will be covered in a lesson														1												
Scheduled	Timed (Duration to take the course)																										

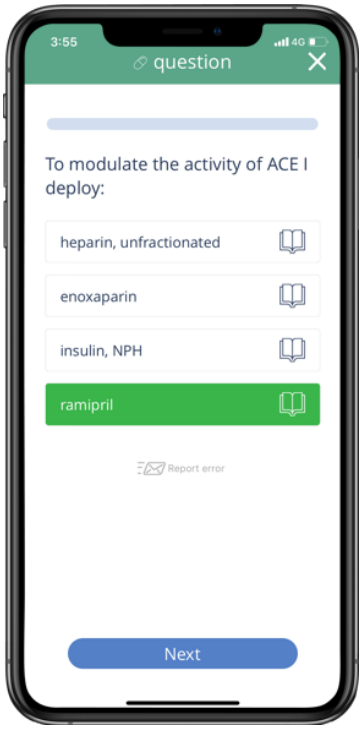
C. Drug questions template

Screen content[1]	Additional information & explanations
	• This screen is used to select drugs for learning. It conveys no knowledge other than which drugs affect which System. • Drugs are grouped primarily according to the System and secondarily from A-Z.
	**KE: A** • Normal function of MM (e.g. ACE) • ACE is a MM that can be inhibited by the drug Ramipril. • Some drugs (e.g. amiodarone) have more than one MM. In such cases, the LU should begin with one of them taken randomly. • "Decreases" / "increases" correspond to arrows ↓ and ↑, respectively, which precede the name of the pertinent MM (e.g. ↓ ACE).



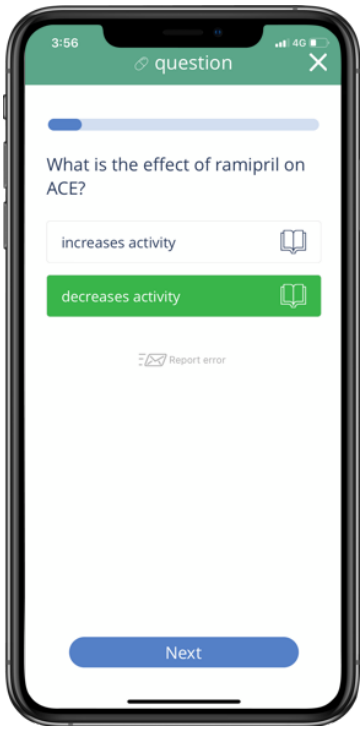
Question: A1

- Assesses the relationship Drug → MM → MM-G
- The correct option is the Group Classification of the "ACE" MM.
- Descriptions of the individual Groups are Concepts. These articles are used when a user clicks on the book for further information as shown in the picture. Please note that this only applies to this question.
- Books lead to MM-G descriptions in Concepts
- "More information" button leads to Drug card



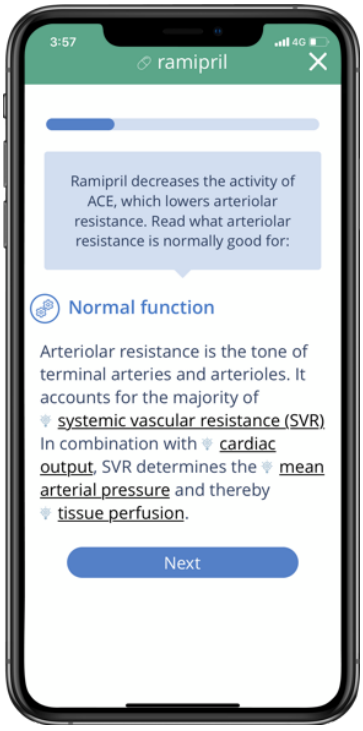
Question: A2

- Assesses the relationship MM → Drug.
- A MM can be modulated by one or more Drugs e.g. Ca^{+2} channels can be modulated by amiodarone, verapamil, and amlodipine. The drugs entered into the editor mask of the MM "ACE". It is identical with one of the drugs listed in the MM cards e.g. "ACE" in the "Show me" of the app.
- Which drug constitutes the correct option is defined by the LU (i.e. by which drug is currently being learned).
- Other drugs targeting this MM should excluded from the list of incorrect answer choices
- Book links lead to drug cards
- No "More information" button

	**KE: B** • Therapeutic modulation of MM
	**Question: B1** • Assesses the relationship Drug → MM → ↓↑ (increased or **decreased**) activity • The correct response is the arrow specified under ACE name prefix (↓, ↑) • This question necessitated splitting MMs that have both increased and decreased activity in two entries e.g. “adrenoceptors” and “myocardial contractility” because they both ↓ and ↑ activity • For MMs that are split only one is included in the LU, the other is excluded from the admin • Books lead to the card of the drug this LU is about • No “More information” button

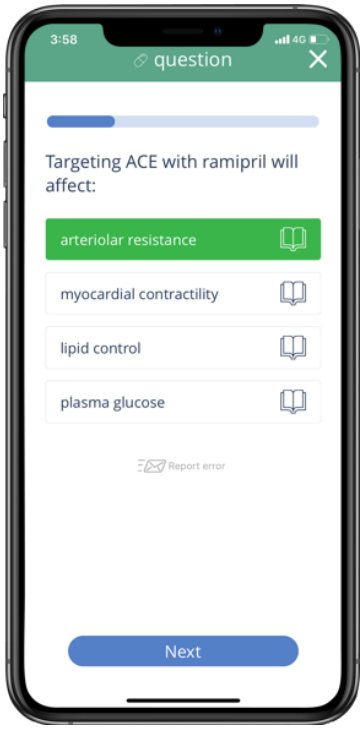
Question: B2

- Assesses the relationship Drug → MM → ↓↑ (increased or **decreased**) activity.
- A Drug targets one or more MM e.g. amiodarone targets 3 MMs. These are listed in the drug cards in the "Show me" of the app.
- Which MM constitutes the correct option is defined by which MM is currently being learned.
- Other MMs targeted by this drug should be excluded from the list of incorrect answer choices.
- Book links lead to MM cards
- No "More information" button



KE: C

- CM normal function
- Arteriolar resistance is a CM.
- The words "decreases" / "increases" correspond to arrows ↓ and ↑, respectively, which precede the name of the pertinent CM.

<table>
<tr>
<td> 
</td>
<td>Question: C1

Assesses the relationship Drug → MM → CM.
For each CM the targeting MM is listed in the admin. Note that a CM can be targeted by more than one MM. The correct option is the MM being taught “Arteriolar resistance”.
Some MMs target more than one CM e.g. ACE targets 3 CMs.
Which CM constitutes the correct option is defined by which CM is currently being learned
Remove all other CMs targeted by MM from the list of wrong answer choices.
Books lead to CM cards.
“More information” button leads to Drug card
</td>
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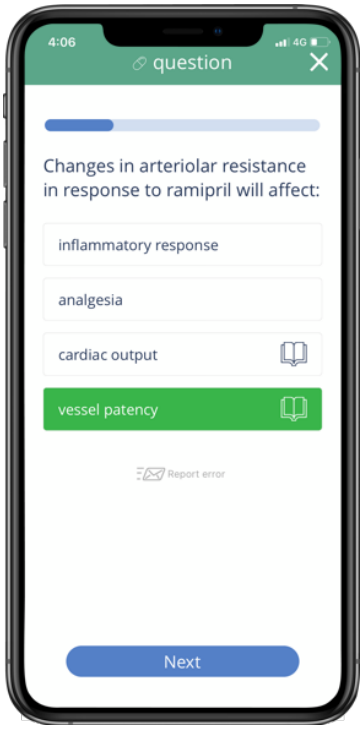
<tr>
<td> 
</td>
<td>Question: C2

Assesses the relationship (Drug → MM →) CM → CM-G.
The correct option is the Group Classification of the CM in being learned.
Books lead to CM-G descriptions such as vessel patency.
“More info” button leads to a Drug card.
</td>
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</table>

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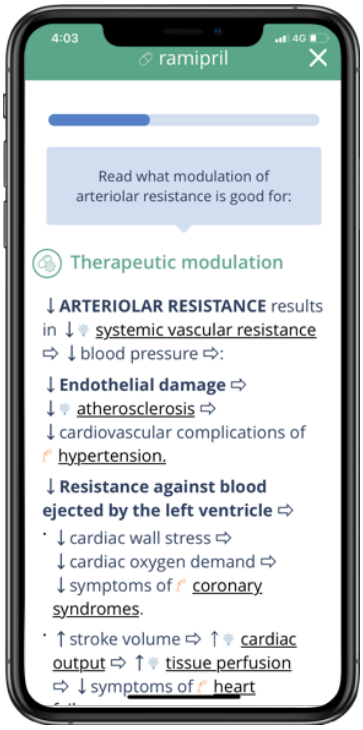
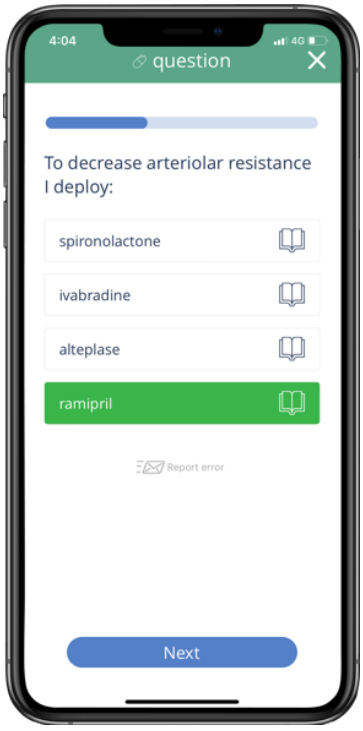
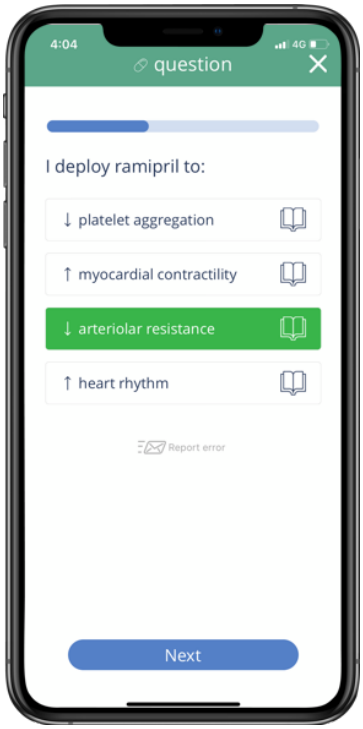
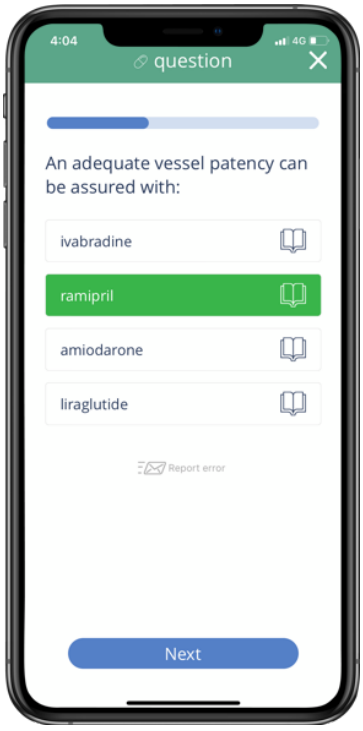
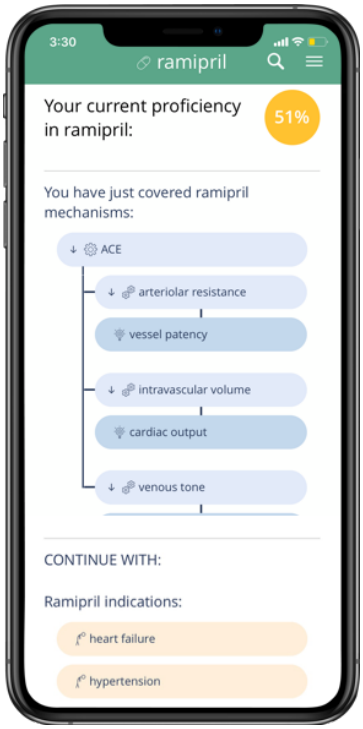
<tr>
<td> 
</td>
<td>KE: D
• CM Therapeutic modulation.</td>
</tr>
<tr>
<td> 
</td>
<td>Question: D1
• Assesses the relationship → ↓↑ activity → CM → (MM →) Drug.
• Note that a CM can be targeted by more than one Drug
• Which Drug constitutes the correct option is defined by which Drug is currently being learned. The drugs are listed in the CM cards in the “Show me” of the app.
• Remove all other Drugs targeting this CM from the list of wrong answer choices.
• Books should lead to Drug cards
• No “More information” button</td>
</tr>
</table>

<table>
<tr>
<td> 
</td>
<td>Question: D2

Assesses the relationship Drug → (MM →) CM → ↓↑ activity
A Drug (through a MM) can target more than one CM. E.g. Ramipril has one MM (ACE) and 3 CMs.
The correct option is the CM being learned “Arteriolar resistance”.
Other possible correct options (CMs) should be excluded from the pool of wrong choices.
Books lead to CM cards
“More information” button leads to Drug card
</td>
</tr>
<tr>
<td> 
</td>
<td>Question: D3

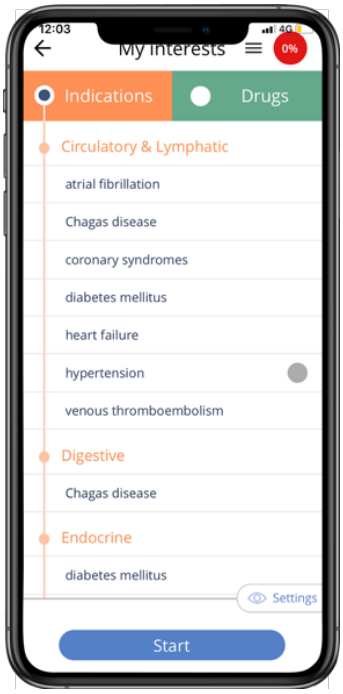
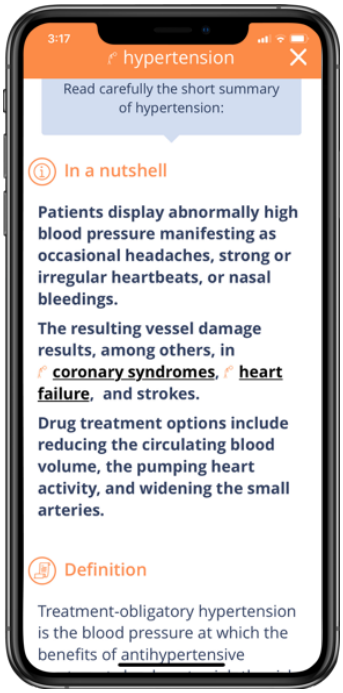
Assesses the relationship CM-G → (CM → MM →) Drug.
This question can have more than one correct answer. The CM-G 'Vessel Patency' can be modulated by a total of 9 drugs acting via 3 CMs
The correct response is the drug being learned
Books lead to Drug cards
No “More information” button
</td>
</tr>
</table>

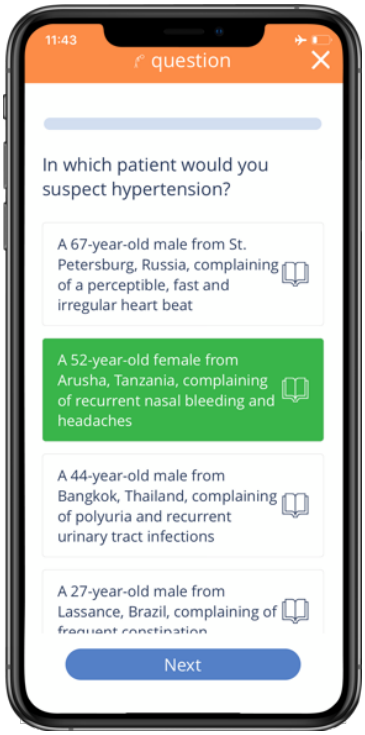
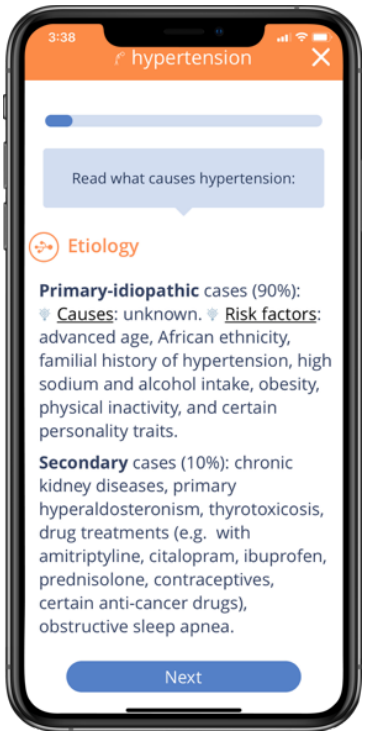


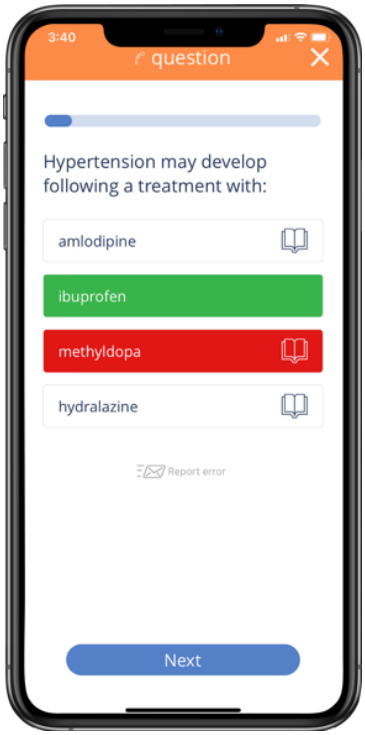
Summary screen:

- This screen provides a list summary of the mechanisms covered in a respective LU.
- The learner is provided an opportunity to continue with indications treated by the drug that was learned or continue with another drug LU preselected

D. Indications questions template

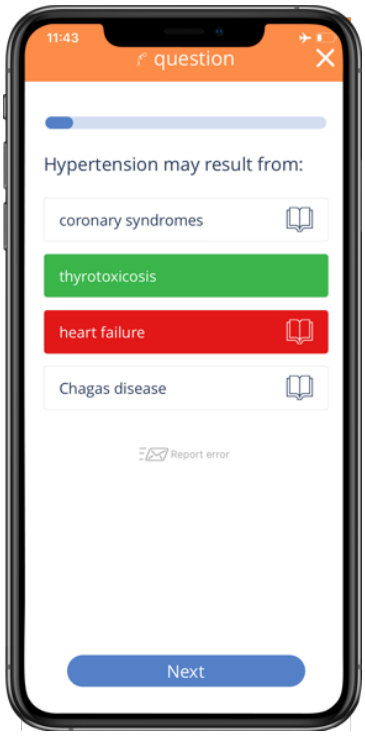
Screen content	Additional information & explanations
	• This screen is used to select Indications for learning. It conveys no knowledge other than which Indications belong to which Specialty. • Indications are grouped primarily according to the Specialty and secondarily from A-Z.
	**KE: A** • Hypertension is an Indication (Disease) • Note here that two KEs are shown (In a nutshell and Definition)

<table>
<tr>
<td> 
</td>
<td>Question: A1
Interrogates the recall of the most important symptoms. It puts the description of a disease in a real-life context - that of a specific patient described in simple terms.
Patient descriptions are titles of “case scenarios” entered via admin
Books lead to Indication cards
No “More information” button</td>
</tr>
<tr>
<td> 
</td>
<td>KE: B
Etiology</td>
</tr>
</table>



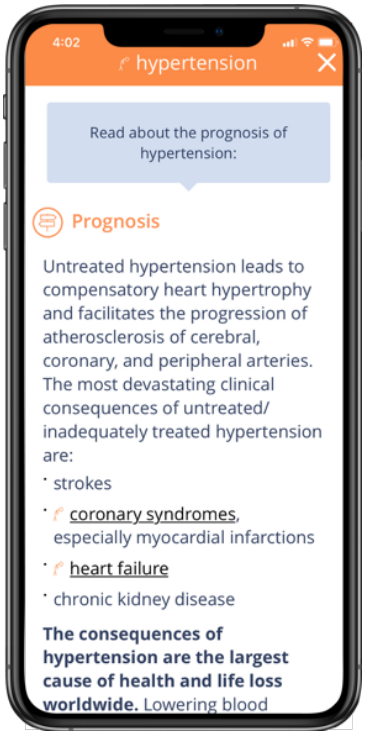
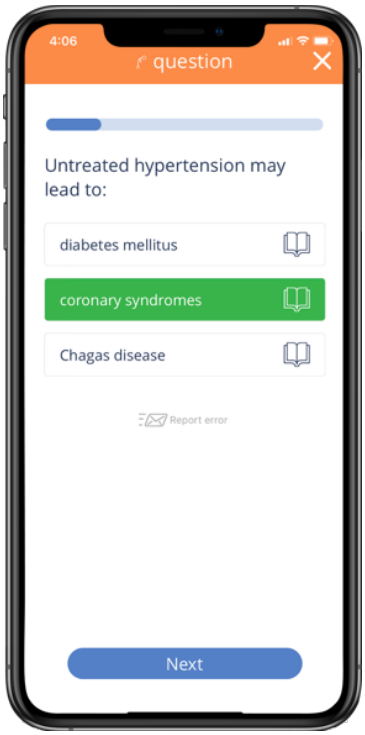
Question: B1

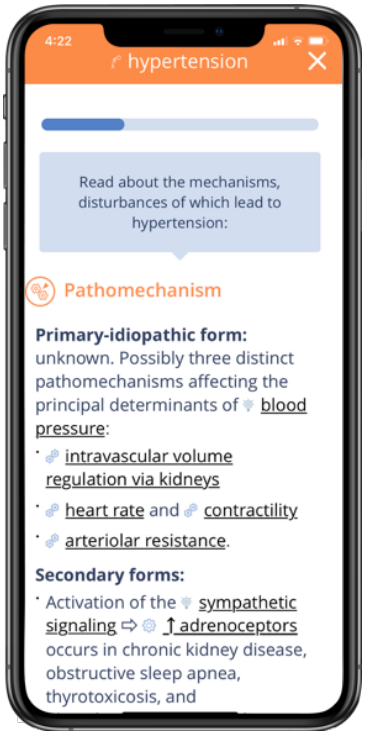
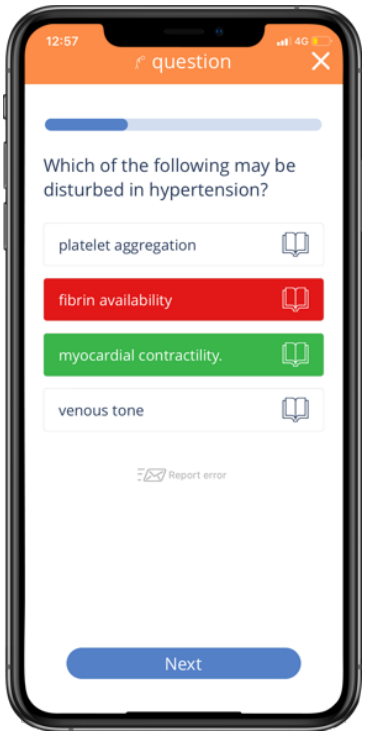
- Interrogates Indication → Drugs causing.
- An Indication can be caused by more than one Drug, listed under "drugs cause condition" in the Indications editing panel in Admin.
- The correct option is one random Drug (from the "drugs cause condition" list), the others should be excluded from the list of wrong answer choices.
- Not all Indications are caused by Drugs. Therefore, some Indication LUs will not have this question.
- Books lead to Drug cards.
- "More information" button leads to "Etiology" KE.



Question: B2

- Interrogates Indication → Indications causing.
- An Indication can be caused by more than one Indication, listed under "conditions cause condition" in the Indications editing panel in Admin.
- The correct option is one random Indication (from the "conditions cause condition" list), the others should be excluded from the list of wrong answer choices.
- Not all Indications are caused by Indications. Therefore, some Indication LUs will not have this question.
- Books lead to Indication cards.
- "More information" button leads to "Etiology" KE.

	**KE: C** ● Prognosis
	**Question: C1** ● Interrogates Indication → Indication(s) resulting. ● An Indication can cause one or more Indications, listed under "condition leads to conditions" in the Indications editing panel in Admin. ● The correct option is one random Indication (from the "condition leads to conditions" list), the others should be excluded from the list of wrong answer choices. ● Not all Indications cause Indications. Therefore, some Indication LUs will not have this question. ● Books lead to Indication cards. ● "More information" button leads to "Prognosis" KE

<table>
<tr>
<td> 
</td>
<td>KE: D
• Pathomechanisms</td>
</tr>
<tr>
<td> 
</td>
<td>Question: D1
• Interrogates Indication → CMs disturbed.
• These CMs are listed in the Indications editing panel in “Clinical Mechanisms cause condition” in Admin.
• The correct option is one random CM, the others should be excluded from the list of wrong answer choices.
• Not all Indications have disturbed CMs. Therefore, some Indication LUs will not have this question.
• Books lead to CM cards.
• “More information” button leads to “Pathomechanisms” KE.</td>
</tr>
</table>

<table>
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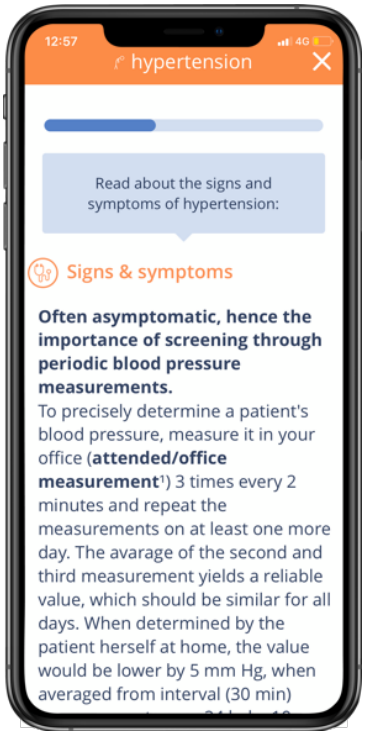
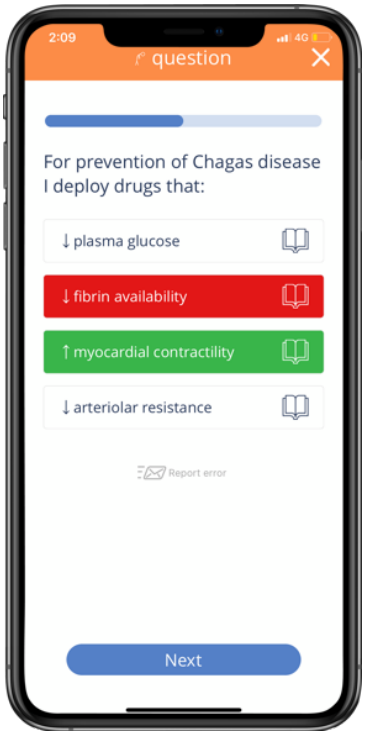
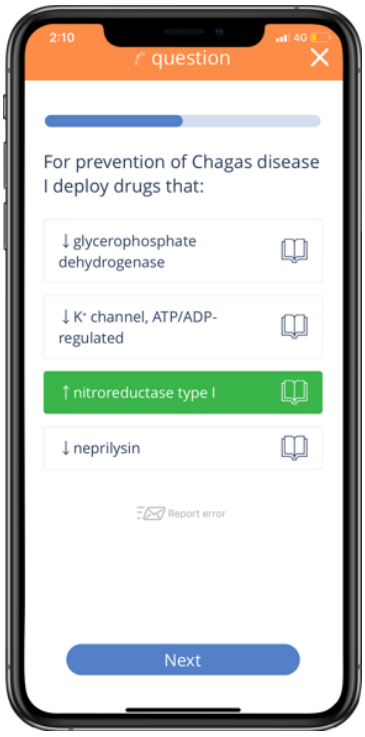
<td> 
</td>
<td>KE: E
• Signs & symptoms
• This KE currently has no questions following it. Therefore, this KE should be shown with a “next button” leading to the next KE.</td>
</tr>
<tr>
<td> 
</td>
<td>KE: F
• Prevention is one of four possible therapy goals.
• Only one question of each type (F1, F2, F3) should be deployed in a LU, even if more are possible due to multiple CMs, MMs and Drugs involved in this therapy goal.
• Some Indications e.g. hypertension have no Drugs for prevention. In such cases, the KE should be shown with a “next button” leading to the next KE.
• The indication for this KE is Chagas disease</td>
</tr>
</table>

	**Question: F1** • Interrogates Therapy goal → Prevention → CM targeted • The CMs are from **"This involves"** entry. Note that there can be multiple CMs. • The correct option is one random CM, the others should be excluded from the list of wrong answer choices. • Books lead to CM cards. • "More information" button leads to "Prevention" KE.
	**Question: F2** • Interrogates Therapy goal → Prevention → MM targeted • The MMs are from the **"via"** entry. Note that there can be multiple MMs. • The correct option is one random MM, the others should be excluded from the list of wrong answer choices. • Books lead to MM cards. • "More information" button leads to "Prevention" KE.

<table>
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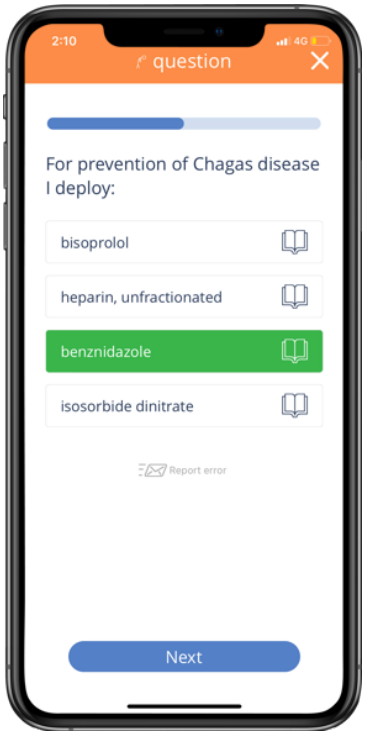
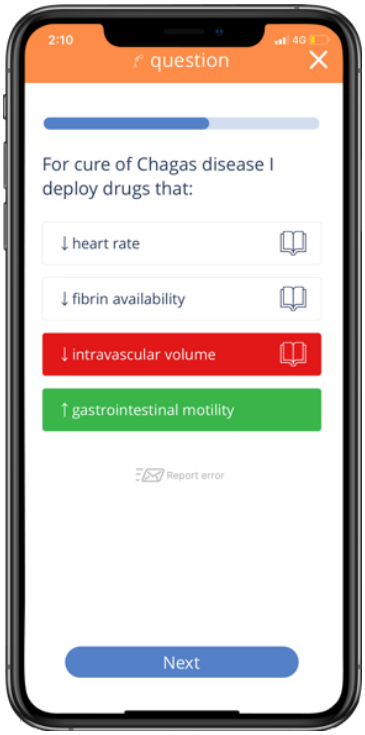
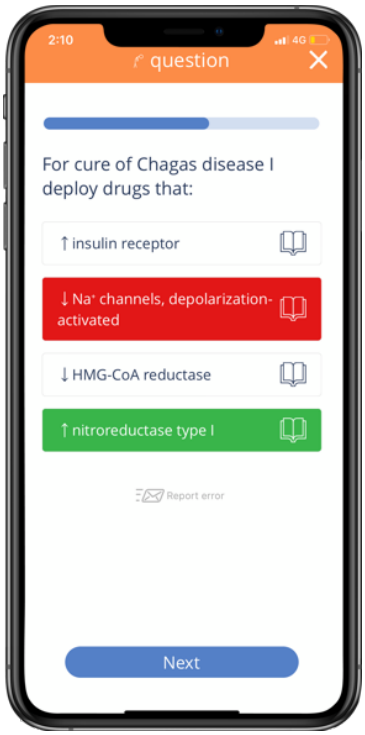
<td> 
</td>
<td>Question: F3
Interrogates Therapy goal → Prevention → Drug treating
The Drugs are from “with” entry. Note that there can be multiple Drugs.
The correct option is one random Drug, the others should be excluded from the list of wrong answer choices.
Books lead to Drug cards.
“More information” button leads to “Prevention” KE.</td>
</tr>
<tr>
<td> 
</td>
<td>KE: G
Cure is one of four possible therapy goals.
Only one question of each type (G1, G2, G3) should be deployed in a LU, even if more are possible due to multiple CMs, MMs and Drugs involved in this therapy goal.
Some Indications have no Drugs for cure. In such cases, the KE should be shown with a “next button” leading to the next KE.
The indication for this KE is Chagas disease</td>
</tr>
</table>



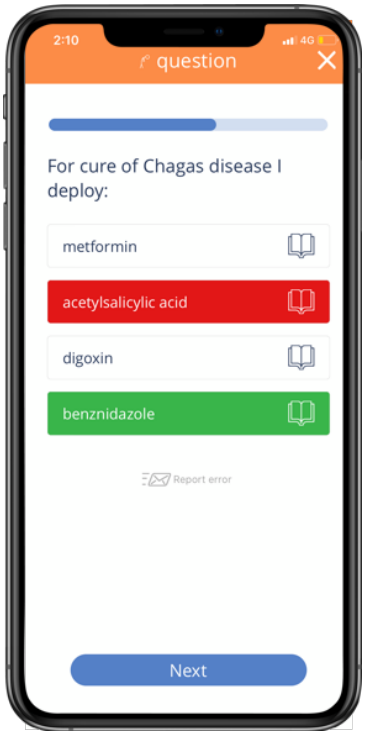
Question: G1

- Interrogates Therapy goal → Cure → CM targeted
- The CMs are from **"This involves"** entry. Note that there can be multiple CMs.
- The correct option is one random CM, the others should be excluded from the list of wrong answer choices.
- Books lead to CM cards.
- "More information" button leads to "Cure" KE.



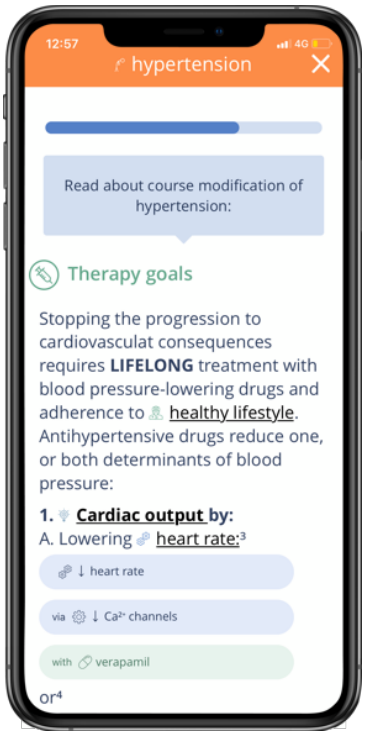
Question: G2

- Interrogates Therapy goal → Cure → MM targeted
- The MMs are from the **"via"** entry. Note that there can be multiple MMs.
- The correct option is one random MM, the others should be excluded from the list of wrong answer choices.
- Books lead to MM cards.
- "More information" button leads to "Cure" KE.



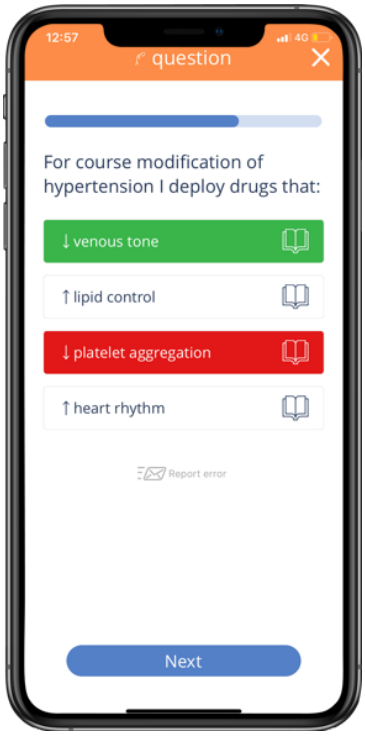
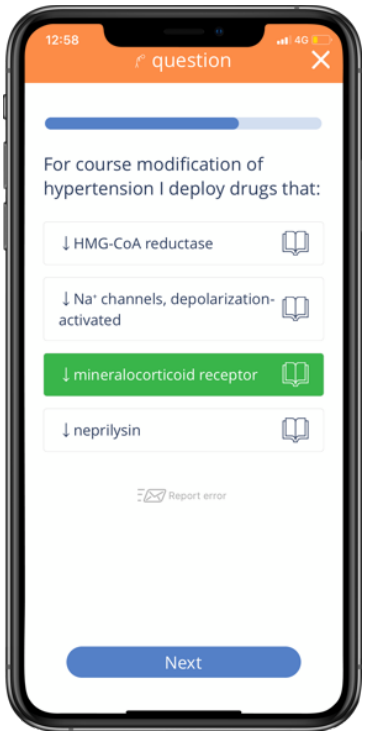
Question: G3

- Interrogates Therapy goal →Cure →Drug treating
- The Drugs are from **"with"** entry. Note that there can be multiple Drugs.
- The correct option is one random Drug, the others should be excluded from the list of wrong answer choices.
- Books lead to Drug cards.
- "More information" button leads to "Cure" KE.



KE: H

- Course Modification is one of four possible therapy goals.
- Only one question of each type (J1, J2, J3) should be deployed in a LU, even if more are possible due to multiple CMs, MMs and Drugs involved in this therapy goal.
- Some Indications have no Drugs for prevention. In such cases, the KE should be shown with a **"next button"** leading to the next KE.

<table>
<tr>
<td> 
</td>
<td>Question: H1
● Interrogates Therapy goal → Course Modification → CM targeted
● The CMs are from “This involves” entry. Note that there can be multiple CMs.
● The correct option is one random CM, the others should be excluded from the list of wrong answer choices.
● Books lead to CM cards.
● “More information” button leads to “Course Modification” KE.</td>
</tr>
<tr>
<td> 
</td>
<td>Question: H2
● Interrogates Therapy goal → Course Modification → MM targeted
● The MMs are from the “via” entry. Note that there can be multiple MMs.
● The correct option is one random MM, the others should be excluded from the list of wrong answer choices.
● Books lead to MM cards.
● “More information” button leads to “Course Modification” KE.</td>
</tr>
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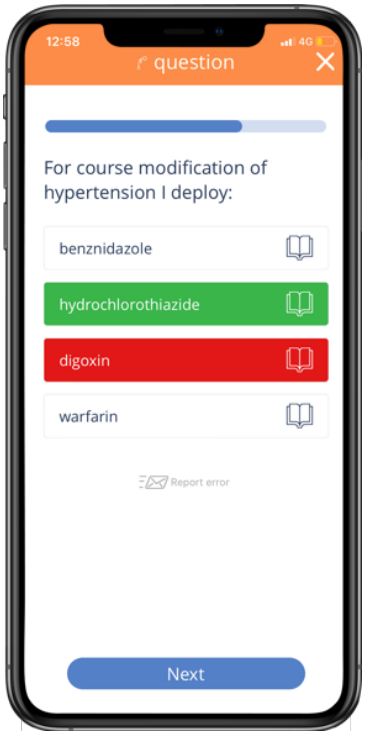
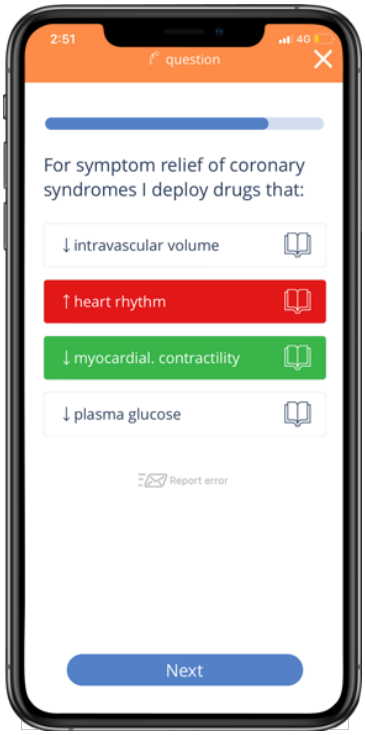


Question: H3

- Interrogates Therapy goal → Course Modification → Drug treating
- The Drugs are from **"with"** entry. Note that there can be multiple Drugs.
- The correct option is one random Drug, the others should be excluded from the list of wrong answer choices.
- Books lead to Drug cards.
- "More information" button leads to "Course Modification" KE.

KE: J

- Symptom relief is one of four possible therapy goals.
- Only one question of each type (J1, J2, J3) should be deployed in a LU, even if more are possible due to multiple CMs, MMs and Drugs involved in this therapy goal.
- Some Indications e.g. hypertension have no Drugs for Symptom relief. In such cases, the KE should be shown with a **"next button"** leading to the next KE.
- The indication for this KE is coronary syndrome disease

<table>
<tr>
<td> 
</td>
<td>Question: J1

Interrogates Therapy goal → Symptom relief→ CM targeted
The CMs are from “This involves” entry. Note that there can be multiple CMs.
The correct option is one random CM, the others should be excluded from the list of wrong answer choices.
Books lead to CM cards.
“More information” button leads to “Symptom relief” KE.
</td>
</tr>
<tr>
<td> 
</td>
<td>Question: J2

Interrogates Therapy goal → Symptom relief → MM targeted
The MMs are from the “via” entry. Note that there can be multiple MMs.
The correct option is one random MM, the others should be excluded from the list of wrong answer choices.
Books lead to MM cards.
“More information” button leads to “Symptom relief” KE.
</td>
</tr>
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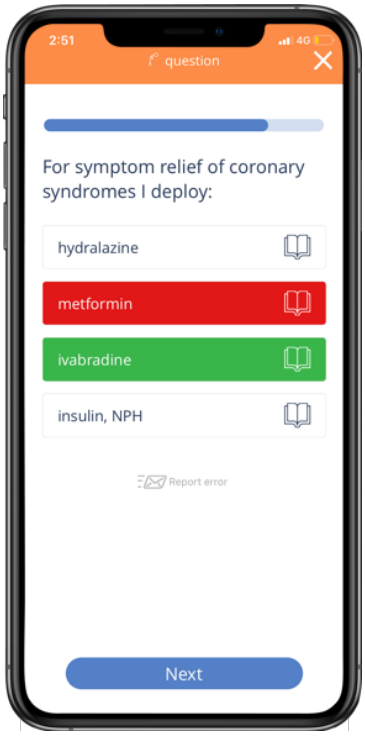
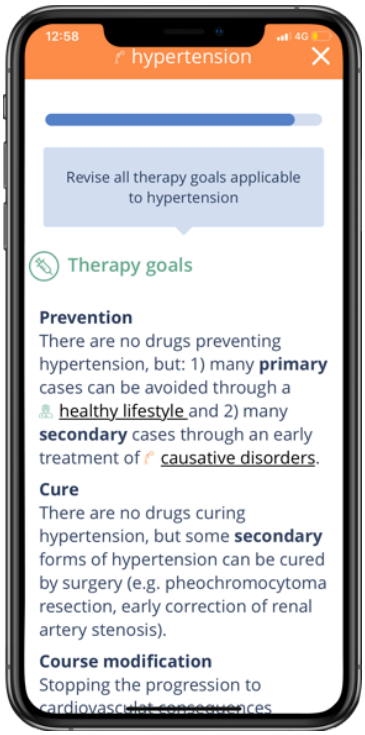


Question: J3

- Interrogates Therapy goal → Symptom relief → Drug treating
- The Drugs are from **"with"** entry. Note that there can be multiple Drugs.
- The correct option is one random Drug, the others should be excluded from the list of wrong answer choices.
- Books lead to Drug cards.
- "More information" button leads to "Symptom relief" KE.

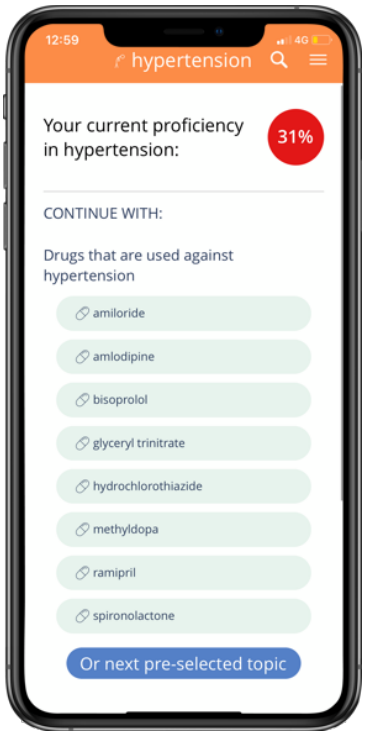


KE: K

Therapy goals

Question: K1

- Interrogates Indication → pharmacotherapy achievable Therapy goal
- Pharmacotherapy achievable Therapy goals are those that have drug lists. These are the correct answer choices.
- Unlike other questions, here all the 4 therapy goals are listed in the answer choices.
- The learner can choose only one answer choice. All correct Therapy goals should be highlighted in green after answering the question.
- Books lead to "Therapy goals" cards in the Pharmacology group in the Library.
- "More information" button leads to "Therapy goals" KE.



Summary screen:

- This is a summary screen of an Indication LU.
- The learner is provided an opportunity to continue with drugs that treated Indication just learned or continue with another Indication LU preselected

E. User acceptance survey

We need your feedback to improve and further develop PharmaFrog. The survey takes a maximum of 5 minutes to complete and it is anonymous.

This survey is conducted on behalf of the International Union of Basic and Clinical Pharmacology (IUPHAR). We will not share your responses with any other third party.

Contact: info@PharmaFrog.org

There are 14 questions in this survey.

1. How much time in total have you spent using PharmaFrog? *

Please choose **only one** of the following:

- Not at all
- Less than 1 hour
- 1 to 6 hours
- 6 - 24 hours
- More than 24 hours

2. Only answer this question if the following conditions are met:

Answer was 'Less than 1 hour' *or* '1 to 6 hours' *or* '6 - 24 hours' *or* 'More than 24 hours' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)

	Useless **1**	**2**	**3**	**4**	**Extremely useful** **5**
What is your overall rating of PharmaFrog?					

3. Is PharmaFrog easy to use?

Only answer this question if the following conditions are met:
Answer was 'More than 24 hours' *or* '6 - 24 hours' *or* 'Less than 1 hour' *or* '1 to 6 hours' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)
Choose one of the following answers
Please choose **only one** of the following:

- Yes
- No

Make a comment on your choice here:

4. **Is the structure of PharmaFrog understandable?**

Only answer this question if the following conditions are met:

Answer was 'More than 24 hours' *or* '6 - 24 hours' *or* '1 to 6 hours' *or* 'Less than 1 hour' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)
Choose one of the following answers
Please choose **only one** of the following:

- Yes
- No

Make a comment on your choice here:

5. Rate the amount of information on diseases and drugs in PharmaFrog. *

Only answer this question if the following conditions are met:
Answer was 'More than 24 hours' *or* '6 - 24 hours' *or* '1 to 6 hours' *or* 'Less than 1 hour' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)
Choose one of the following answers
Please choose **only one** of the following:

- Too little
- Just right
- Too much

6. What would you add to Pharmafrog?

Only answer this question if the following conditions are met:
Answer was 'More than 24 hours' *or* '6 - 24 hours' *or* 'Less than 1 hour' *or* '1 to 6 hours' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)

7. Would you recommend PharmaFrog to a colleague?

Only answer this question if the following conditions are met:
Answer was 'Less than 1 hour' *or* 'More than 24 hours' *or* '1 to 6 hours' *or* '6 - 24 hours' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)
Choose one of the following answers
Please choose **only one** of the following:

- Yes
- No

Make a comment on your choice here:

8. Where are you located? *

Only answer this question if the following conditions are met:
Answer was '6 - 24 hours' *or* 'Less than 1 hour' *or* '1 to 6 hours' *or* 'More than 24 hours' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)
Choose one of the following answers
Please choose **only one** of the following:

- List of countries

9. What is your main profession?

Only answer this question if the following conditions are met:
Answer was 'Less than 1 hour' *or* '1 to 6 hours' *or* '6 - 24 hours' *or* 'More than 24 hours' at question '1 [Q1]' (How much time in total have you spent using PharmaFrog?)
Choose one of the following answers
Please choose **only one** of the following:

- Student
- Medical doctor
- Nurse
- Pharmacist
- Educator
- Other

10. Which discipline? *

Only answer this question if the following conditions are met:
Answer was 'Student' at question '9 [Q12]' (What is your main profession?)
Choose one of the following answers
Please choose **only one** of the following:

- Doctor of medicine
- Nursing
- Pharmacy
- Other

11. Speciality

Only answer this question if the following conditions are met:
Answer was 'Medical doctor' at question '9 [Q12]' (What is your main profession?)
Choose one of the following answers
Please choose **only one** of the following:

- Allergy & immunology
- Anesthesiology
- Dermatology
- Diagnostic radiology
- Emergency medicine
- Family medicine
- Internal medicine
- Medical genetics
- Neurology
- Obstetrics and gynecology
- Ophthalmology
- Pathology
- Pediatrics
- Physical medicine & rehabilitation
- Preventive medicine
- Psychiatry
- Radiation oncology
- Surgery
- Urology

- Other

12. Area of practice

Only answer this question if the following conditions are met:
Answer was 'Pharmacist' *or* 'Nurse' *or* 'Medical doctor' at question '9 [Q12]' (What is your main profession?)
Check all that apply
Please choose **all** that apply:

- Primary level
- Secondary level
- Tertiary level
- Private institution
- Public institution
- Other:

13. How long have you been working in your field? *

Only answer this question if the following conditions are met:
Answer was 'Nurse' *or* 'Medical doctor' *or* 'Educator' *or* 'Pharmacist' at question '9 [Q12]' (What is your main profession?)
Choose one of the following answers
Please choose **only one** of the following:

- Less than 2 years
- 2 to 5 years
- 6 to 10 years
- More than 10 years

14. Year of study

Only answer this question if the following conditions are met:
Answer was 'Student' at question '9 [Q12]' (What is your main profession?)
Choose one of the following answers
Please choose **only one** of the following:

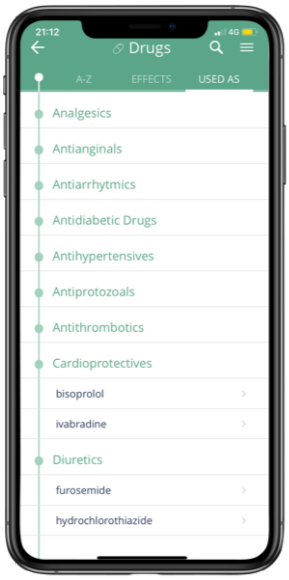
- 1
- 2
- 3
- 4
- 5
- Intern

Thank you for taking the time to complete this survey. Your input is valuable. If you have any further questions regarding this survey, please contact info@pharmafrog.org

Submit your survey.
Thank you for completing this survey.

F. Article lists

A



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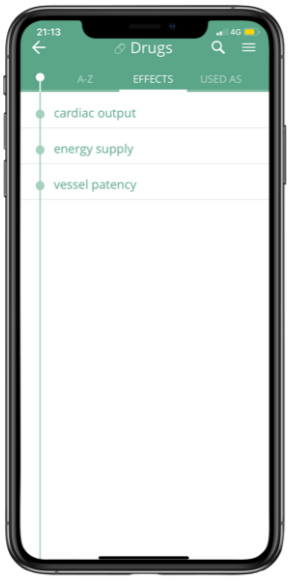

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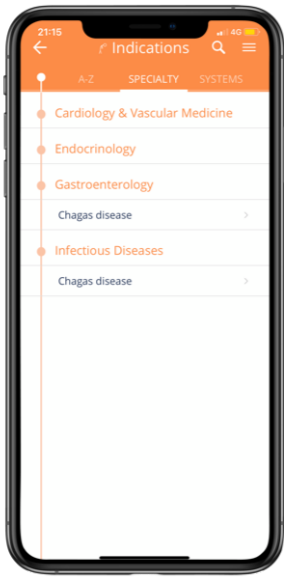

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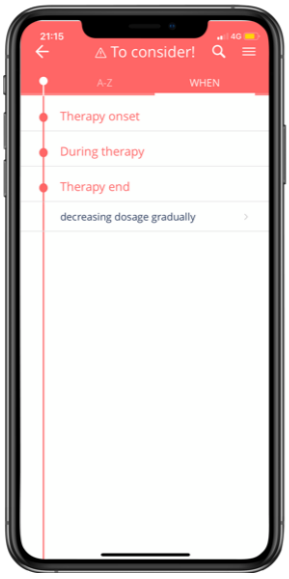

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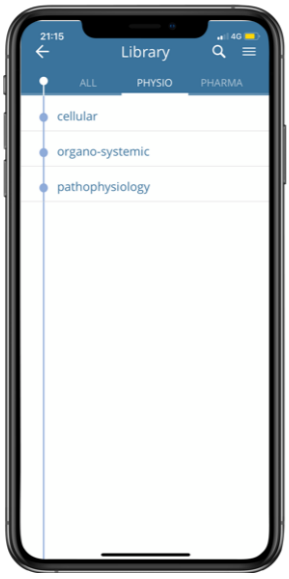

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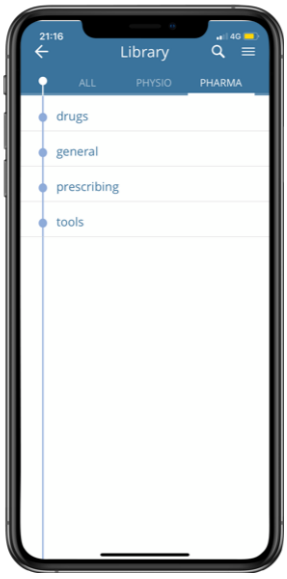


G. Functionality testing protocol

This section provides a guide of evaluating the major functionalities of PharmaFrog

I. Publishing databases

Status	Show in app for	
	Admin /Editor	Users
Create new article, do not check the 'ready' status	No	No
Check the 'ready' status of the article	Yes	No
Check the 'Published' checkbox and the article in Admin → Publish → Review page and then click save	Yes	Yes
Check published without selecting any articles	Yes	Yes
Uncheck the 'ready' status of an article, do not publish database	No	Yes
Uncheck the 'ready' status of an article, publish database	No	No
Delete an article with 'ready' status	No	No

Table 13: Content publication criteria

II. TEACH ME

- From home screen, open TEACH ME
- Select Drugs/Indications units of interest
- Under setting, activate 'Lowest proficiency first' to be presented with drugs/indication units sorted with least proficiency first otherwise units will be presented randomly irrespective of their proficiency.
- Clicking start, a series of KEs interspersed with questions should be presented for one LU at a time
- At the end of each LU proficiency score of the unit is presented. In addition, for each Drug LU, a list of learned mechanisms and the Indications the drug is used to treat is displayed, and for each Indication LU a list of drugs that are used to treat it are listed. You may continue learning another Drug/Indication LU from the previously selected Drugs/Indications list or with one of the Indications/Drugs in the summary page.
- Terminate a LU by clicking on X in the upper left corner or by closing the app. Upon returning to TEACH ME, you should get an alert that prompts you to either continue with the last

interrupted session or quit. Clicking No will return you to LU selection screen and clicking yes, should take you to the last KE that was accessed.

III. QUIZ ME

- From home screen, open QUIZ ME
- Under setting, activate ‘Lowest proficiency first’ to be presented with questions with the least proficiency otherwise questions will be presented randomly irrespective of their proficiency.
- A quiz of ten questions from the selected LUs will be presented.
- At the end of the quiz, you will get feedback on how many questions were answered correctly. For each attempted LU you will get feedback of percentage proficiency change and the overall proficiency in colored dots.

IV. REFRESHER

- Open teach me or quiz me
- Under settings, make sure refreshers are set to daily or weekly
- Attempt a quiz or take a TEACH ME session to schedule a refresher
- Go to phone settings, move the date forward by one day/week, depending on the momentary refresher settings
- A REFRESHER notification should pop up on the phone screen
- Open the refresher from the phone notification window

H. Proficiency fine-tuning concept

The time spent reading an individual KE will be obtained using the current app version. This time will then be used to calculate an average reading speed (words per minute). Below is the detailed description of how the 30% will be achieved for Indications and Drugs respectively.

For Indications: The number of words (n) will be summarily counted for all KEs, i.e. In a nutshell, Definition, Etiology, Prognosis, Pathomechanism, Signs and symptoms, Therapy principles, and Additional Information.

A learner may boost the proficiency in an Indication by up to 30%, depending on the time spent reading it and the amount of words contained. How is the exact boost calculated?

- The average reading speed is Rs (words per minute)
- The minimum required reading time Tr (min) = n/Rs accordingly
- The actual reading time is Ta (min)
- Proficiency boost per reading session Pb (%) = Ta/Tr x 30%.
- Proficiency boost cannot exceed 30% even if Ta>Tr

Example*: The aforementioned KEs of an indication card altogether have 600 words (*Figure 16*).*

- *Minimum reading time required Tr = n/Rs = 600/150 = 4”00”“, assuming the average reading time of 150 words per minute*
- *The user spends 2”00”“ minutes reading that card.*
- *Proficiency boost: Pb (%) = Ta/Tr x 30% = 2”00”“/4”00”“ x 30% = 15%*
- *The proficiency increases by 15% for each KE that is included in LUs, Quizzes, or Refreshers, i.e. for Definition and Etiology, Prognosis, Pathomechanism, Signs and symptoms, and Therapy principles.*

The illustration below (Figure 48) shows how Indication proficiency is generated altogether:

- is generated through Teach Me (LUs), Quiz Me, and Refresher activities (on the left in the illustration, with blue lines converging on this Indication proficiency), and
- It is boosted through the Lookup/Reading activity described above (on the right in the illustration). Note that reading-derived boost, indicated by red-dotted arrows, must be fed into the KE and then their specific questions, since it is the questions which primarily undergo “forgetting effect” and trigger Refreshers.

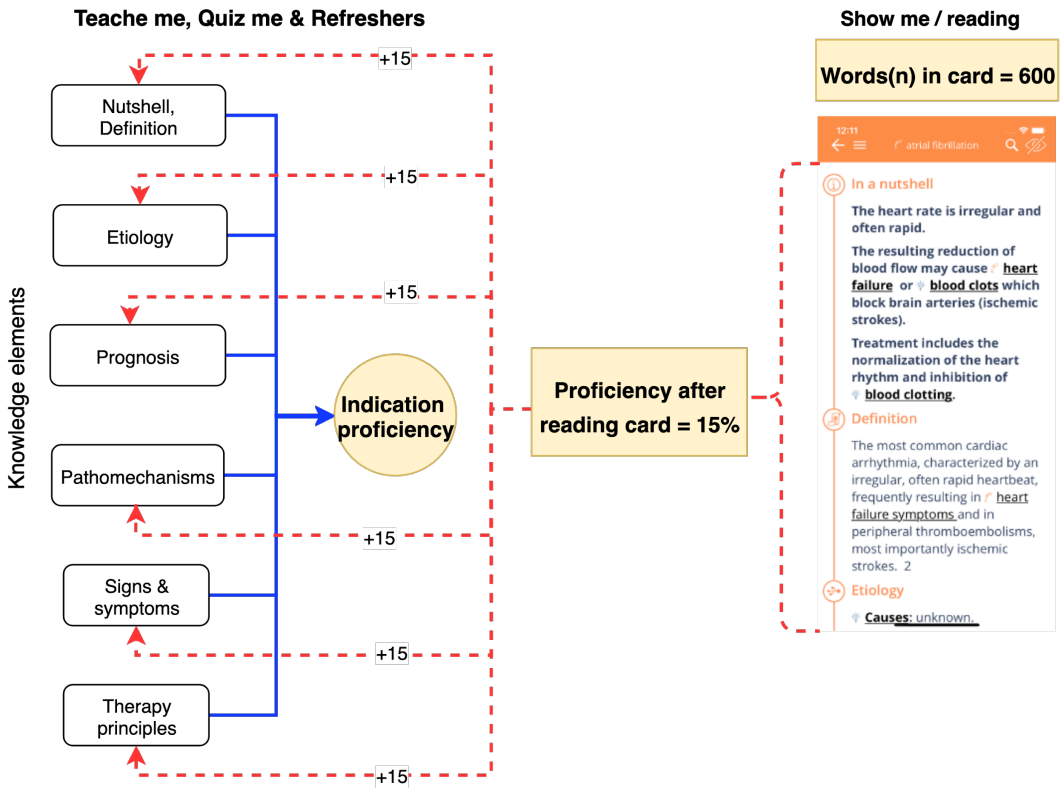
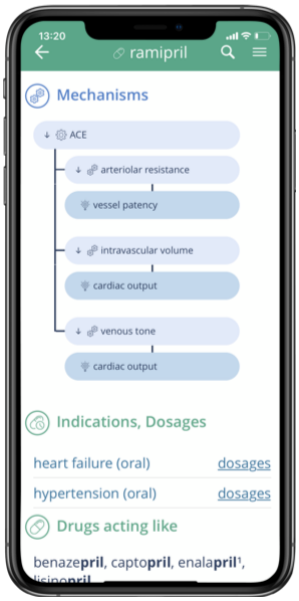


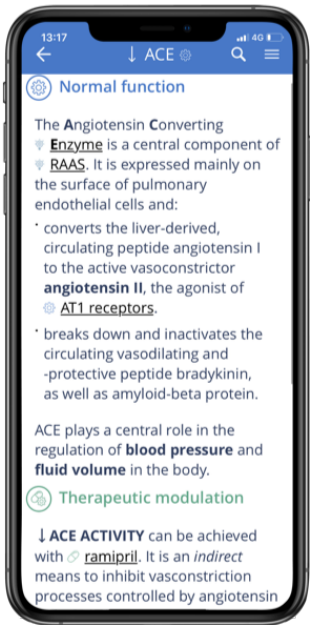
Figure 48: An example of proficiency gains from reading an Indication card.

For drugs: A learner may boost the proficiency in a Drug by up to 30%, depending on the time spent reading it and the number of words it contains. How is the exact boost calculated?



1. Read a Drug card e.g. Ramipril
   - Proficiency contribution is up to 10%.
   - The minimum required reading time Tr (min) is, 1 minute
   - The actual reading time is Ta (min)
   - Proficiency boost per reading session Pb (%) = Ta/Tr x 10%.
   - Proficiency boost cannot exceed 10% even if Ta>Tr

   The finally calculated proficiency contributes to all KEs for all mechanisms of that particular drug



2. Read a mechanism card, e.g. ACE for Ramipril

For each mechanism card count the number of words (n) in the following KE: Normal Function and Therapeutic modulation

- Proficiency contribution is up to 20%.
- The minimum required reading time Tr (min) = n/Rs
- The actual reading time is Ta (min)
- Proficiency boost per reading session Pb (%) = Ta/Tr x20%.
- Proficiency boost cannot exceed 20% even if Ta>Tr

The finally calculated proficiency contributes to all KEs (Normal Function and Therapeutic modulation) of that particular mechanism in all associated drugs

The illustration below (Figure 49) shows how Drug proficiency is generated:

- is generated through “Teach me” on the right in the illustration.
- Note that reading-derived boost is indicated by red-dotted arrows for MMs and green-dotted arrows for CMs and must be fed into the associated KEs. Also note that boosts derived from reading drug cards (item 1, above), indicated by blue-dotted arrows, are fed into KEs of all mechanisms listed in this card.

- Note that proficiency boosts may contribute to more than one Drug, e.g. venous tone boosts candesartan, isosorbide dinitrate, nitroglycerin, and Ramipril (see the venous tone card)

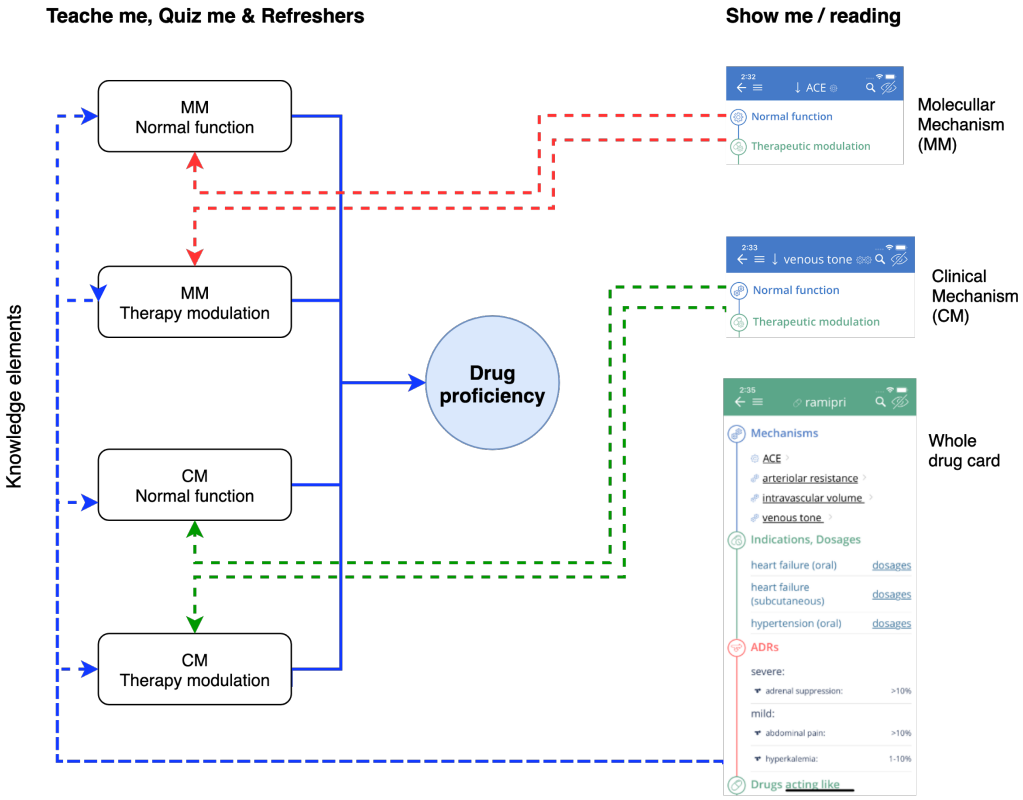


Figure 49: Illustration of proficiency gains from reading drug associated KEs

I. Algorithms for scheduling repetition

1. The Pimsleur Method: The learner is reminded of the new word at intervals increasing in length by a factor of approximately 5, i.e. after approximately 5 sec., 25 sec., 2, 10 and 50 minutes, 5 hours, 1 day, 5 days, 20 days and so on (Pimsleur (1967).

2. The Leitner System: The spacing intervals double, i.e. they increase, but at a slower rate compared to the Pimsleur Method. However, items forgotten since the last practice are assigned a previous (i.e. shorter) spacing interval until the next check. (Leitner., 1972).

3. SuperMemo: SuperMemo Relies on the learner's history of reviewing a concept (i.e number of repetitions, and intervals in days) and rating on a scale of 0-5 how well she/he knew the concept (Godwin-Jones, 2010, Wozniak, 2005).

4. Half-Life Regression: A machine learning-based spacing algorithm that extends the exponential forgetting curve conceptualized by Hermann Ebbinghaus using a log-linear model of memory strength (Settles and Meeder, 2016). This algorithm is currently being implemented in the language learning platform Duolingo, replacing the Leitner System used in the first version released in 2012. It was reported to improve the daily engagement of students by 12% (Settles and Meeder, 2016).

5. Memorize: Builds upon the Half-Life Regression through using a linear stochastic differential equation with jumps to express dynamics of forgetting (Tabibian et al., 2017). It differs from Half-Life Regression by considering that "each session contains a single review event for each item because the reviews in each session take place in a very short time and it is likely that after the first review, the user will recall the item correctly during that session". In contrast, Half-Life Regression considers each session to contain multiple review events for each item. The pitfall of this algorithm is that it has not yet been applied in real life.

6. Spaced Repetition via Model-Free Reinforcement Learning: A scheduling algorithm for spaced repetition software that uses model-free reinforcement learning with neural network function approximation. Preliminary experiments on simulated students produced better results than SuperMemo and the Leitner system (Reddy et al., 2007).