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An Overview of Technology Availability to Support Remote Decentralized Clinical Trials

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***Abstract*—**Developing new medicine and health solutions and improving patient health currently rely on the successful execution of clinical trials, which generate relevant safety and efficacy data. For their success, recruitment and retention of participants are some of the most challenging aspects of protocol adherence. Main barriers include: i) lack of awareness of clinical trials; ii) long distance from the clinical site; iii) the burden on participants, including the duration and number of clinical visits, and iv) high dropout rate. Most of these aspects could be addressed with a new paradigm, namely the Remote Decentralized Clinical Trials (RDCTs). Furthermore, the COVID-19 pandemic has highlighted additional advantages and challenges for RDCTs in practice, allowing participants to join trials from home and not depending on site visits, etc. Nevertheless, RDCTs should follow the process and the quality assurance of conventional clinical trials, which involve several processes. For each part of the trial, the Building Blocks, existing software and technologies were assessed through a systematic search. The technology needed to perform RDCTs is widely available and validated but is yet segmented and developed in silos, as different software solutions address different parts of the trial and at various levels. The current paper is analyzing the availability of technology to perform RDCTs, identifying gaps and providing an overview of Basic Building Blocks and functionalities that need to be covered to support the described processes.

***Keywords*—**Architectures and frameworks for health informatics systems, clinical trials, information and communications technology, remote decentralized clinical trials, technology availability.

I. Introduction

TECHNOLOGY is increasingly incorporated in clinical trials, which constantly evolve, moving towards more innovative models and efficient and effective execution. Applications with graphical user interfaces have been extensively used in clinical trials with a positive impact on the efficiency and satisfaction, but yet barriers and challenges emerge [1]. Other technological components widely used include Electronic Health Records (EHR), mobile apps and wearable devices, proving new insights and reducing costs of clinical trials [6]. Mobile technology, in particular, is constantly increasing, allowing more efficient assessment of new treatments [4]. Artificial Intelligence (AI), Machine learning, Deep Learning and Internet of Things (IoT) technologies are expected to expedite multiple aspects of trials and provide novel, previously inaccessible digital biomarkers [8]. While traditional clinical trials are evolving with technology, so do RDCTs for which technology shows much promise to facilitate remote communications, automated processes with fewer on-site visits, deeper insights, and improved outcomes [2]. Yet, technology is widely varied and segmented in silos, requiring much research and even integration to carry out all the diverse steps and processes during an RDCT.

In this study, a technology scan was performed in search of technologies to further enable the transition and transformation of traditional trials to technology-enhanced RDCTs. The scanning of technology is divided into Basic Building Blocks (BBBs) which correspond to different phases in an RDCT and will enable technology selection for pan European RDCT pilot in the framework of the "Trials@Home: Centre of Excellence for RDCTs" project.

Trials@Home (https://trialsathome.com) is an Innovative Medicines Initiative 2 (IMI2) project comprising 31 international partners from academia, small and medium-sized enterprises (SMEs), private foundations, patient organizations, and industry. The Trials@Home (T@H) consortium aims to explore opportunities to move clinical trials from the conventional clinic setting into the participant's usual surroundings by identifying and making use of digital technologies and other operational innovative approaches. These technologies will be used to run a pan-European pilot study to compare the scientific and operational quality of RDCTs with conventional and hybrid trial approaches.

II. Related Work

Previous work has assessed various types of technology for a variety of the steps and processes in a clinical trial.

To begin with, a systematic review of the use of technology for the recruitment process, namely Clinical Trial Recruitment Support Systems (CTRSS) reveals that they increase recruited patients and recruitment efficiency [5]. It also highlights issues

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such as the importance of the integration of such systems with the existing infrastructure and workflow of clinical care providers.

Data management software systems are also being incorporated, in order to effectively support clinical data management dimensions and, based on review [9], there are no systems that fully cover the data management dimensions of clinical trials. Significant dimensions mentioned in those systems are data collection, entry, report, validation and security maintenance.

The quality of clinical trials has also been studied, showing that a wide variety of trial monitoring practices are being used by clinical trial involved organizations [7]. The survey provided to organizations shows that quality assessment relied mostly on clinical trial data to assess site performance. Some 12% of organizations even use centralized monitoring to replace on-site visits.

While the aforementioned technologies have been employed to enhance "traditional" trials, they may also be used in RDCTs. Regarding technology suitable explicitly for RDCTs, blockchain is one of the most prevalent ones. Blockchain technologies are also being incorporated in some clinical trial areas to simulate scenarios in healthcare processes and health information exchange [10]. Additionally, they are used for managing and monitoring data in multi-site clinical trials in comparison with traditional data management approaches [3].

While many reviews and individual studies have investigated technology and systems for particular steps of a trial, software-solutions that cover all the steps of a clinical trial and especially an RDCT could not be found, as will be shown in the results section.

III. Methods

From high-level ideas of the project, it was required to define seven BBBs with concrete visions and features for the technology and services needed to roll out the envisioned RDCT. The definition of all activities within a BBB was also performed.

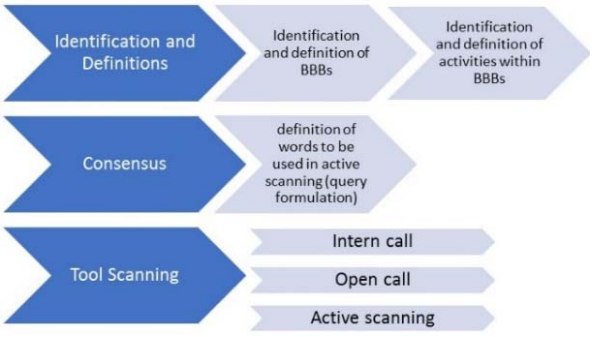

Fig. 1 Overview of the scanning process

The defined BBBs and activities were used to provide guidance for scanning of software, hardware and technologies. Thus, the scanning process was primarily oriented towards the BBBs. The BBB definition was performed in three stages which can be seen in Fig. 1.

Within the first stage, a workgroup created an initial model for BBBs with related activity definitions. The workgroup comprised a wide range of expertise and perspectives. Construction and discussion of definitions were continuously carried out over several weeks. Due to COVID-19 and the international setting of T@H, the definition process within the first stage was performed exclusively through weekly online calls - replacing even annual physical meetings.

In the second stage, specialized workgroups were established. These groups focused on single BBBs and were asked to create visions for their building blocks. Moreover, part of their task was to develop a recommendation on how activities within a BBB could be performed in an RDCT and what kind of systems would be able to support these activities. Another task of the specialized workgroups was to perform reviews for the definitions and quality criteria for the assessment of technologies.

In the third stage, after reaching a consensus for the definitions, the workgroups proceeded with the query formulation used in the active scanning phase and what types of computer systems or technologies should be chosen within the scanning process.

Once the building blocks and activities were defined, a variety of methods was used to perform the scanning rounds for suitable RDCTs technologies. Online scanning for technology and information request of recognized software and hardware provider are two examples of these methods.

Additionally, an internal and external Request for Information (RFI) was published. In the process of RFI, we asked project partners to submit their RDCT technologies. Moreover, we opened a submission (open) call for other project parties and vendors. Furthermore, we performed an active search (scanning) for new technologies that support RDCTs. To gain this result, a workgroup of academia and European Federation of Pharmaceutical Industries and Associations (EFPIA) project members with an interest and experience in technology research was formed. The scanning task, as shown in Fig. 2 was divided into a sequence of subtasks, whereby each sequence was started for each BBB.

We conducted seven scanning rounds (one per BBB) with a duration of two to four weeks for each to search for software tools. Each member of the scanning team was assigned to scan for software in the respective BBBs, thereby focusing on a specific activity within this BBB. Each activity was assigned to at least two persons coming from different organizations, so that the search-bias is minimized, and the variety of tools found is broadened. Fig. 2 shows the described design of the scanning process.

IV. Results

In this chapter, the results of the Building Block definition process and the active scanning tasks are shown.

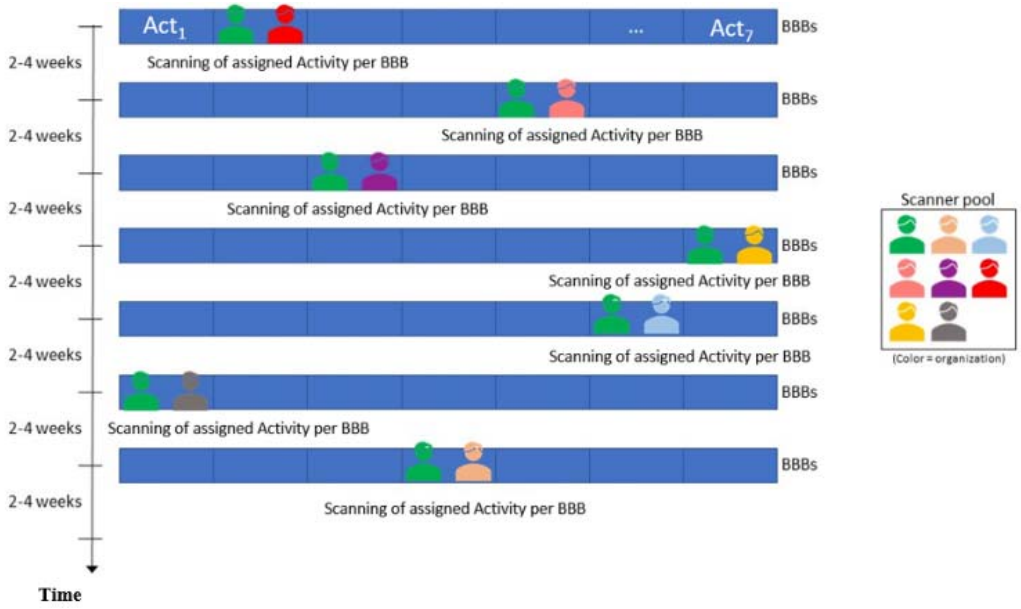

Fig. 2 Design of the Scanning Task from the perspective of a single organization, which is shown in green and on the left in each row

TABLE I
BBB DEFINITIONS

Building Block	Definition
Setup & Design	This Building Block defines the phase in which the clinical trial planning, feasibility and infrastructure are prepared, submitted and designed to allow successful trial execution.
Recruitment & Enrollment	This Building Block defines the RDCT phase in which suitable potential participants are identified and attracted. After initial contact has been established, suitability of patients is assessed, and patients deemed suitable enter the trial.
Intervention & Follow Up	This Building Block includes all activities that gather study data and/or perform interventions according to study protocol.
Closeout & Reporting	This Building Block includes all activities to end the trial, ensuring that all activities have been completed, all materials have been accounted for and decommissioned and results are published to appropriate locations.
Data Acquisition & Processing	This Building Block defines the phase in which all study data (participant demographics, device data, sample results, image data and preliminary analyses etc.) are stored and managed. Both patient's and clinician's perspectives are taken into consideration. Data generated during the clinical trial are stored securely, complying with the protocol and the GCP and ensuring the anonymization of the participant, as well as the integrity and quality of the data. Additionally, in this phase data is checked, verified, transformed and analyzed.
Operation & Coordination	This Building Block includes all processes related to the operational conduct of the study.
Patient Engagement	This Building Block includes all processes to keep patients continuously engaged in the trial.

A. Building Block and Activity Definition

The building block definition agreed by the consortium is shown in Table I.

Within the following step, relevant activities and definitions of the activities were identified and defined. The activities enabled the classification of software systems and tools during the scanning process. An overview of the BBBs and their respective activities can be found in Fig. 3. While some of the BBBs include more than 10 activities (Setup & Design, Operation & Coordination, Patient Engagement), all other BBBs included about six to eight activities.

While most of the activities were defined prior to the scanning, some activities were discovered during the scanning process. The resulting activities for each BBB and its definitions were evaluated through the consortium.

During the scanning progress, a research of software solutions, tools and libraries was conducted, and all items were assessed according to supported activities. There was a broad variety of supporting systems. While some activities are supported by several tools, other activities remained without any related software product. A detailed description is given within the next section.

B. Software Scanning Results

The results of the active scanning process were collected and summarized partly manually and partly automated via the statistics software R [11]. For each BBB, the mean and standard deviation of the number of tools per activity were calculated and can be found in the header of Tables III-IX.

Throughout the scanning results across all BBBs, 323 tools from 268 vendors, covering 43 out of 64 activities, were found to be relevant. The total of Tools, Vendors, and (covered) Activities per BBB can be seen in Table II.

TABLE II
BBBS: LIST OF ACTIVITIES

BBB	Tools	Vendors	Activities total	Activities supported
Setup & Design	104	91	11	9
Recruitment & Enrollment	17	16	8	8
Intervention & Follow Up	11	11	6	4
Closeout & Reporting	53	53	6	4
Patient Engagement	49	48	12	6
Operation & Coordination	14	14	13	6
Data Collection	68	57	8	6

Overall, the highest number of tools per Activity can be found in Setup & Design (Table III), Closeout and Reporting

(Table IV), and Data Collection (Table IX). The smallest set of tools per Activity are observed in Operation & Coordination (Table VIII), where for a set of 8 activities not a single software solution was obtained.

Only one BBB, namely Recruitment & Enrollment, could be covered completely having an average coverage of 4 tools per activity.

TABLE III
NUMBER OF SOLUTIONS: SETUP & DESIGN (10 +/- 10)

Activity	Number of Solutions
Protocol Development	30
Supply Chain Management	23
Site Startup	18
Operational Feasibility and Assessment	15
Technology Setup	9
Regulatory And Ethics Approval	5
Trial Registration	5
Operational Setup	4
Creation of ICF	1
Study Branding	0
Obtain Ethics and Regulatory Approval	0

TABLE IV
NUMBER OF SOLUTIONS: RECRUITMENT & ENROLLMENT (4 +/- 3.5)

Activity	Number of Solutions
IMI Supply (Wearables)	10
Participant Outreach	9
Participant Education	5
Pre-Screening	1
Obtaining Informed Consent	1
Screening	1
Randomization	1
Patient Technology Enablement	1

TABLE V
NUMBER OF SOLUTIONS: INTERVENTION & FOLLOW UP (2 +/- 2)

Activity	Number of Solutions
Telemedicine Visits	4
Clinic Visits	4
Self-Intervention & Self-Monitoring	2
IMP-Adherence Monitoring	1
Home Health Visits	0
IMP-Supply & Re-Supply	0

TABLE VI
NUMBER OF SOLUTIONS: CLOSEOUT & REPORTING (10 +/- 11.5)

Activity	Number of Solutions
Scientific Dissemination of Study Results	29
Publishing of clinical study results	16
Publishing of operational study results	13
Producing Study Report	1
Decommissioning	0
Archiving	0

Since most of the software products that are identified during the scanning process are rather specific to a certain activity, there is almost no overlap among the tool sets found for each BBB. Hence, we also investigated the number of vendors that occur in multiple BBBs.

TABLE VII
NUMBER OF SOLUTIONS: PATIENT ENGAGEMENT (4.5 +/- 7)

Activity	Number of Solutions
Provide patient satisfaction surveys	16
Provide direct patient messaging	16
Create patient engagement plan	15
Patient-HCP interaction and communication	7
Provide patient recruitment and retention incentives	2
Consult participant and/or caregiver advisory board	1
Social listening and patient landscape analysis	0
Patient advocacy group mapping	0
Provide updates to patients throughout the trial	0
Patient concierge service or travel reimbursement (where applicable)	0
Introducing behavioral incentives	0
Patient social community establishment	0

TABLE VIII
NUMBER OF SOLUTIONS: OPERATION & COORDINATION (1.5 +/- 2)

Activity	Number of Solutions
Safety (data) management	6
Study Oversight	6
Operational Analytics	3
Clinical Monitoring	1
Inspection Facilitation	1
Manage Protocol and GCP Deviations	1
Performance monitoring	0
System approval facilitation	0
Documentation management	0
Home Health visit management	0
Telemedicine visit management	0
Regulatory management	0
Vendor management	0

TABLE IX
NUMBER OF SOLUTIONS: DATA COLLECTION (10 +/- 10)

Activity	Number of Solutions
Management of study-generated data,	26
Clinical Data Repository Management	24
Gathering & Management of Real-Life-Data	10
Data Analysis	8
Data Transformation & Standardization	6
eCRF and System Query Design	5
Data Reconciliation and Query Management	0
Database Lock	0

As can be seen in Fig. 4, 18 vendors can be found in more than one BBB, only four occur in the maximum number of three BBBs.

In Table X, the size of the smallest subset of tools and vendors to cover all activities per BBB is shown. The numbers are collected using a greedy algorithm approach [12]. Leaving aside the possible overlap of tools and vendors among the BBBs, a total number of 32 Tools or 27 Vendors would be needed to cover all 43 Activities.

Table XI shows the set of activities that are covered by the top-5 tools that cover the most activities. Selecting the top-5 tools, a total of 15 Activities could be covered.

TABLE X
SMALLEST SUBSET TO COVER ALL ACTIVITIES PER BBB

BBB	Number of covered activities	Smallest Subset of Vendors	Smallest Subset of Tools
Setup & Design	9	6	8
Recruitment & Enrolment	8	5	6
Intervention & Follow Up	4	3	3
Closeout & Reporting	4	3	3
Patient Engagement	6	3	4
Operation & Coordination	6	4	4
Data Collection	6	3	4
Sum	43	27	32

V. CONCLUSION

The presented work shows the results of our search for software systems used for RDCTs clustered by different BBB categories along the process of clinical trials. The number of results of Information and Communications Technology (ICT) components available on the market varies depending on the BBBs and different activities addressed in the BBB.

Studying the results, the largest number of 105 available tools is observed in the BBB Setup & Design. Relatively low numbers of components could be found for the BBBs Intervention & Follow Up (11), Operation & Coordination (14), and Recruitment & Enrollment (17). All other BBBs show numbers between 49-68 ICT technology providers.

TABLE XI
COVERAGE OF ACTIVITIES BY THE TOP-5-TOOLS

Top_n-Tool	Activity
1	Management of study-generated data
1	Create patient engagement plan
1	Provide direct patient messaging
1	Patient-HCP interaction and communication
2	Participant Outreach
2	Obtaining Informed Consent
2	Participant Education
3	Patient Technology Enablement
3	Supply Chain Management
3	IMI Supply (Wearables)
4	Study Oversight
4	Publishing of operational study results
4	Manage Protocol and GCP Deviations
5	Self-Intervention & Self-Monitoring
5	Clinic Visits

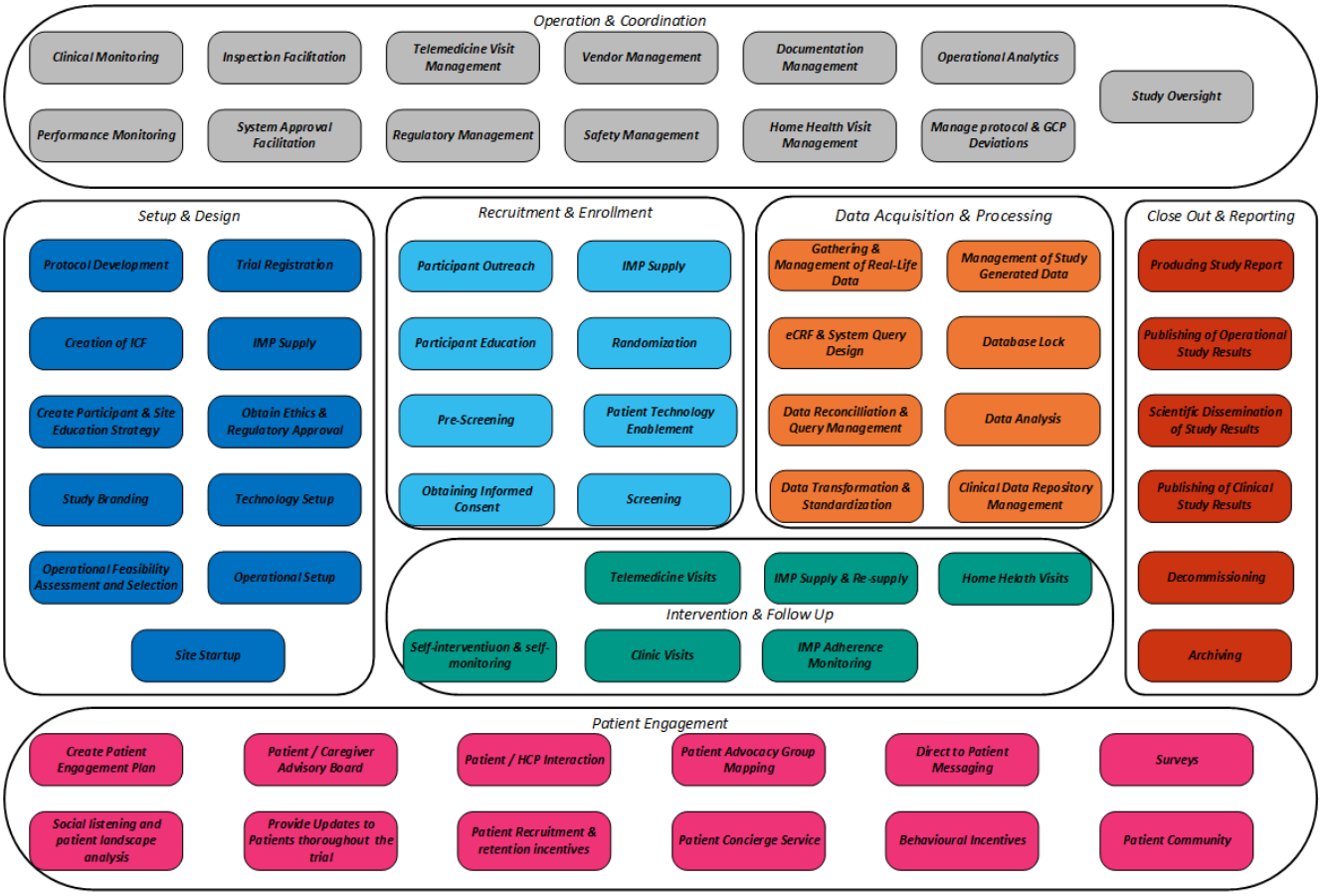

Fig. 3 Overview of resulting Building Blocks and the related activities within each Building Block

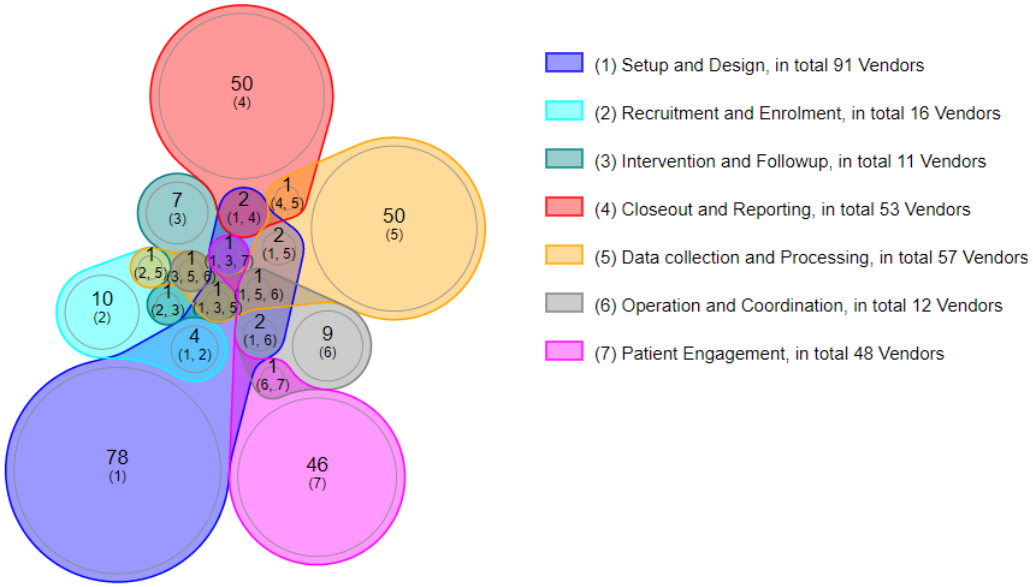

Fig. 4 Venn Diagram showing all vendors grouped by building blocks. The groups are split up into vendors only contributing to one building block (biggest circle) and into circles overlapping with other building blocks. The number of overlaps and the corresponding building block IDs are shown in the respective circles; for better traceability, the overall sum per building block is also shown in the legend

It can be seen that for some specific aspects of RDCTs there are gaps in available technology which gives room for further innovation or for the industry to close these gaps. Gaps may relate to innovative aspects where still a perfect way in RDCTs needs to be found. Other technology aspects in RDCTs might be more straightforward like patient onboarding or an integrated voice-and-video patient consultation. Furthermore, aspects like patient recruitment might need less integration with other components compared to device integration and remote data capture, which might also be an aspect of encapsulated ICT components on the market. These paper results can be used as a reference for technological tools used in an RDCT setting and more research can be conducted, especially for the aspects of the clinical trial that technological tools are yet to be incorporated.

The aim of the project is to provide guidelines as well as criteria (including standards and functional requirements) which we would recommend for ICT components in the different BBBs. The aim must be to provide the option of modular ICT components which can be used in the future to set up RDCTs and to cover different trial use cases with a flexible setup.

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