Technology Support System and Review Process for a Decentralized Clinical Trial: Trials@Home, RADIAL DCT as Case Study

Sten Hanke[1][a], Dimitrios Giannikopoulos[3], Hannes Hilberger[1,2][b], Theresa Weitlaner[1][c] and Bernhard Neumayer[1][d]

[1]*Institute of eHealth, University of Applied Sciences - FH Joanneum, Alte Poststraße 149, Graz, Austria*

[2]*GSRC, Division of Medical Physics and Biophysics, Medical University of Graz, Graz, Austria*

[3]*BAYER AG, Wuppertal, Germany*

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Abstract: Decentralized Clinical Trials (DCTs) revolutionize clinical research by leveraging digital technologies to decentralize various aspects inherent in the traditional clinical trial process like the need for patients' physical presence. DCTs integrate virtual and remote elements for assessments, data collection, and monitoring, prioritizing convenience. However, the integration of diverse stakeholders and technologies poses challenges in delivering timely and effective solutions across all trial sites. Addressing this requires the establishment of a robust technology support system tailored to meet the unique demands of decentralization. This paper outlines the requirements for such a system and shares initial insights gained through the learning process. This system combines a Wiki-like knowledge base with a ticketing system for handling support requests, enabling the creation of topic-specific tickets and ensuring that queries are directed to the appropriate support agents swiftly. The implemented helpdesk system in the RADIAL study exemplifies how combining a comprehensive information resource with a responsive ticketing system not only streamlines supporting processes but also significantly enhances response efficiency and the overall user experience in DCTs. This integrated approach is pivotal in managing the complexities and dynamic nature of DCTs, ensuring that both patients and stakeholders benefit from the efficiency and adaptability of decentralized trials.

1 INTRODUCTION

Decentralized clinical trials (DCT) aim to eliminate the need for study patients to be physically present at the study site for investigations, contributing to increased efficiency, accessibility, and patient-friendliness in clinical research. As technology advances, decentralized approaches are expected to play a more significant role in the future of clinical trials.

This approach broadens the pool of potential patients (de Jong et al., 2022), enhances patient adherence (Jain et al., 2022), and reduces the study's carbon footprint (Subaiya et al., 2011; Holmner et al., 2014).

While these advancements are promising, the reduced on-site presence necessitates a robust support system. This system should provide a continuously accessible knowledge base and direct communication channels with professionals, ensuring stakeholders are well-informed, up-to-date, and equipped to handle hardware or other technical issues effectively.

Effective communication and tracking of technical and process issues are crucial for quality control. Integrating the technology provider's support in a timely and effective manner—from patients to sites to Clinical Research Associates (CRAs) and vendors—is imperative.

Although similar demands exist in conventional clinical trials, DCTs introduce additional challenges due to the integration of different technology providers and increased reliance on patients for using technology. This raises expectations for the usability and technical stability of apps and technologies.

In summary, a technology support system for DCTs should not only promote seamless interaction among stakeholders and technologies but also address the challenge of providing timely solutions to various sites.

[a] https://orcid.org/0000-0003-3833-4252
[b] https://orcid.org/0000-0003-3867-0651
[c] https://orcid.org/0009-0005-7076-2929
[d] https://orcid.org/0000-0002-4439-4799

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Trials@Home's technology support system encompasses all aspects required for barrier-free participation in the RADIAL clinical trial. Given the multitude of stakeholders and roles (patients, site, CRA) in the study, the support system integrates various existing solutions provided by project partners, ensuring an optimized workflow.

Using the RADIAL study as an example, this paper presents an exemplary approach to consolidate available tools into one helpdesk system. The paper details the system's requirements, the RADIAL implementation, the achievement of quality control through automated Key Performance Indicator (KPI) exports, and an issue-tracking process. It also summarizes initial experiences from the study.

2 BACKGROUND

In contemporary clinical trial technology, the integration of Electronic Data Capture (EDC) and Clinical Trial Management Systems (CTMS) has become commonplace. Recent studies, such as the investigation conducted by Zhang et al. (Zhang et al., 2013), underscore a significant rise in electronic data collection facilitated by various self-developed, commercially available, or open-source software solutions. These technological advancements have prompted a reevaluation of the interpretation of ICH E6 and the Good Clinical Practice guidelines by sponsors (Bhatt, 2023).

ICH E6(R2) was amended in 2023 to encourage the implementation of technological advances to enhance the efficiency of clinical trial conduct. The subsequent update, E6(R3), has elevated the guidelines for incorporating state-of-the-art technologies in managing clinical trials (Bhatt, 2023).

The guidelines recommend adapting the use of technology in clinical trial conduct to fit patient's attributes and trial design specifics (Council, 2023). The emphasis on technology within these guidelines has broad implications for all aspects of trial conduct, including quality, ethics, and stakeholder responsibilities (Bhatt, 2023).

The relevance of these guidelines becomes particularly evident with the emergence of DCTs. While the guidelines advocate technology use for various processes, spanning from data acquisition to patient interaction and consent processes, they do not specifically address technology support for issue tracking and helpdesk support involving different stakeholders in DCTs.

In clinical trials, particularly in DCTs, such a support system can play a pivotal role in managing and addressing the varied needs of patients and the involved technologies. DCTs, often spanning different countries and languages, encounter unique challenges like language barriers as well as varying levels of IT proficiency among patients and site users. To address these, a comprehensive support system is essential.

One critical component is a ticketing system. This system allows patients to raise queries, which are then addressed by a dedicated support team. The uniqueness of this system lies in its dual function. Besides resolving individual queries, the support team also contributes to a centralized knowledge base. When a query is resolved, the team develops articles or content related to that issue, enhancing the knowledge base. This proactive approach ensures that frequently asked questions are readily available to all patients, thereby reducing repetitive queries and streamlining the support process.

Quality Assurance (QA) teams should monitor these tickets to identify and mitigate any risks to patient safety or data integrity. This comprehensive oversight ensures that the support system not only addresses current issues but also continuously evolves to enhance the efficiency and safety of the clinical trial process.

Quality assurance (QA) emerges as a pivotal process for effecting quality improvements in the context of technological enhancements. Zhang et al. introduced the QA Issue Tracking System (QAIT), a centralized platform for systematic information collection and management to identify and correct QA errors effectively (Zhang et al., 2013).

A streamlined process for tracking issues and facilitating communication, along with a comprehensive knowledge repository accessible to various stakeholders in DCTs, further enhances risk management.

A strategic evolution in clinical trial monitoring is evident with the adoption of Risk-Based Monitoring (RBM), as reported by Barnes et al. (Barnes et al., 2021). Capitalizing on increased connectivity and data analytics advances, RBM represents a targeted approach to error detection. In complex trial workflows, such as those encountered in DCTs, RBM faces distinct challenges, especially when integrating new technologies and coordinating with multiple stakeholders.

For DCTs, which rely on diverse systems and processes, the imperative, extending beyond conventional clinical trials, is to find mechanisms to reduce costs and establish robust quality control and issue tracking processes.

Agrafiotis et al. demonstrated that centralized monitoring activities have the potential to identify a substantial proportion (95%) of the findings revealed

by on-site monitoring visits (Agrafiotis et al., 2018). This underscores the importance of tracking issues and documentation, particularly in mHealth and home environment technologies, where diverse technologies and vendors are integrated into a singular setup. This complexity heightens the importance of providing comprehensive helpdesk support and knowledge bases for CRAs, sites, and other stakeholders.

DCTs, being relatively novel, present distinct challenges necessitating specialized helpdesk support. The work of de Jong et al., involving interviews with European regulators and assessors of clinical trials, has shed light on challenges related to DCTs, including the use of technical devices and measurements in at-home situations (de Jong et al., 2022). In response, the Trials@Home project has established a knowledge base and a helpdesk technology support system. This system serves the dual purpose of assisting CRAs and sites in navigating technology-supported DCTs and providing a robust tool for quality control, issue tracking, and compliance monitoring.

3 RADIAL CASE STUDY

3.1 The Trials@Home Project

Clinical trials have long been a cornerstone of evidence-based medicine, yet the traditional model poses challenges in terms of patients burden, geographical constraints, and data reliability. The Trials@Home project emerges as an innovative response, seeking to transform this landscape by introducing a decentralized approach to clinical research.

At its core, Trials@Home leverages state-of-the-art digital technologies, mobile medical devices and a Mobile App to facilitate remote data collection. Patients are empowered to contribute to research endeavors from their own residences, alleviating the logistical and time-related burdens associated with on-site visits. The integration of mobile medical devices enables continuous, real-time monitoring, ensuring a comprehensive dataset while bolstering patient engagement and compliance.

The patient-centric ethos underpinning the project not only fosters inclusivity but also addresses disparities in access to healthcare resources. By harnessing the capabilities of mobile medical devices, Trials@Home offers a dynamic platform for researchers to gather high-fidelity, ecologically valid data.

The project further aims to establish a framework for seamless collaboration between clinical investigators, technologists, and patients, ensuring a cohesive research experience.

Through the Trials@Home project, we anticipate not only an evolution in the execution of clinical trials but also a paradigm shift in how we approach patient engagement and data collection in medical research. This endeavor holds the potential to democratize access to research opportunities, drive efficiency, and ultimately, accelerate the development of innovative healthcare solutions.

3.2 RADIAL Design

The RADIAL study, as part of the IMI's Trials@Home initiative, exemplifies the innovation in DCTs. Distinguished by its "bring-your-own-device" (BYOD) methodology, the study integrates conventional, hybrid, and entirely remote trial formats, catering to diverse technological needs. Study patients use their own mobile phones to install the Clinpal® Mobile App to access the study's interfaces. Additionally, patients use mobile medical devices in the form of a Mallya smart cap for insulin injection [1], an AccoCheck glucometer to control blood sugar [2], and a blood pressure meter to measure blood pressure values. The study is designed to test three discrete clinical trial approaches in two different study parts:

- **Part A:**
  - *Arm 1:* Adopts a traditional model with exclusively onsite patient interactions.
  - *Arm 2:* A hybrid model, blending onsite interactions with remote engagements.
- **Part B:**
  - *Arm 3:* A fully remote, decentralized arm, facilitating all patient interactions from their homes, exemplifying the full potential of DCTs in clinical research.

3.3 RADIAL Technology

The scope of RADIAL is facilitated by a range of DCT technologies and devices. Table 1 presents the vendors, DCT technologies utilized, installation types, and their relevance to specific study parts.

3.4 Requirements

In the search for an effective technology support system for a large-scale trial like RADIAL, several key requirements have been identified. The requirements

[1] https://biocorpsys.com/en/our-products/connected-devices/mallya/

[2] https://www.accu-chek.at/

Table 1: Vendors and DCT technologies applied within RADIAL.

Vendor	Technology Component	Installation	Relevant Part(s)
AARDEX	MEMS Adherence Software (MEMS AS®)	Custom	A (arm 2), B
AARDEX	MEMS® Mobile App	Custom	A (arm 2), B
eClinical Health	Radial Study App	Custom	All
eClinical Health	Clinpal® Platform (branded as RADIAL Study Portal)	Configured with custom components	All
Investis Digital	RADIAL Study Website	Custom	B
Signant Health	Smart Signals Telemedicine® (previously 'Virtrial Telemedicine')	Configured with custom components	B
Signant Health	SmartSignals RTSM®	Configured with custom components	All

have partly been derived from findings in the literature (see Chapter 2) and the requirements needed to serve the RADIAL study design. Several tools have been tested based on this. The final selection, the UVdesk open-source helpdesk solution, fulfills most of the requirements, providing a comprehensive ticketing system and knowledge base. Furthermore, it offers the flexibility to adapt the solution to our specific requirements. The final requirements are that the system shall offer a centralized repository of information, including answers to frequently asked questions (FAQs), and provide an adaptable and extensible content management system (CMS). Moreover, system users should be able to contact persons with detailed knowledge on specific topics of the study in a customer support and service-oriented manner. Different roles with varying access permissions to the helpdesk system, such as content creator, ticket agent, or administrator shall be possible to be defined. The requirements specifically identified for RADIAL include consolidating information and knowledge from various channels into a single helpdesk system, exchanging training materials and expertise through eLearning, and imposing restrictions on access to learning resources by requiring a password for the website to prevent general availability.

4 SELECTION OF SUPPORT SYSTEM PLATFORM

RADIAL support system is built on UVdesk, an open-source helpdesk solution [3]. UVdesk provides a fully functional project package, which can be configured to the specific needs of the trial:

- A customizable, user-friendly dashboard for easy access and navigation.
- A helpdesk knowledge base (KB) that can be designed to RADIAL's needs i.e., to support Clinical Research Associates (CRAs) and site staff.
- Backend access for modifying and expanding the knowledge base, using a Content Management System (CMS).
- A dashboard for ticket agents to manage and respond to support requests efficiently and effectively.

Additionally, UVdesk's database structure facilitates the extraction of key performance indicators (KPIs) such as request count, response frequency, and average resolution time, through SQL queries. These metrics can be compiled into a report thereby providing valuable insights into the system's performance and efficiency.

4.1 Customizing the Support System for RADIAL

Figure 1 shows the landing page of the implemented RADIAL helpdesk system after login. Users can search for information and will be suggested related articles containing the search key words in their metadata.

Figure 1 also outlines the structure designed for RADIAL to provide an intuitive navigation, with the first level presenting topics as tiles for easy access. The layout encourages self-service browsing through various folders:

- Frequently Asked Questions (FAQs): Contains categorized answers to common queries from study sites and teams.
- Vendors: Hosts technical and specific documents from organizations providing products or services for RADIAL.
- Site/CRA Training: Includes materials specifically for sites and CRAs, such as Site Initiation

[3]https://www.uvdesk.com/en/opensource/

Visit (SIV) documents and technology manuals.

- Patient Training: Offers training resources for patients in different study arms, covering topics like app usage and medical event reporting.
- Other Categories: Organizes information akin to Site/CRA and Patient training in a topic-based layout, including categories like Informed Consent and Product & Logistics.

In addition, offers a quick search text box as well as quick links to navigate directly to vendor, study, glossary, and to the investigator meeting information.

The Tiles contain multiple categories, which in turn include various articles, linkable across different folders for relevance. Regular discussions in helpdesk scrums also focus on enhancing the Knowledge Base, especially the FAQs, based on emerging ticket issues.

4.2 Support System Roles

To streamline operations, we have established five distinct user roles. Each subsequent role encompasses the permissions of the preceding ones, plus additional capabilities:

- **Content Creators:** Typically, CRAs and technical support staff, they organize and add to the knowledge base. Published content appears on the front-end (Figure 1), while drafts are for internal use.
- **Ticket Creators:** CRAs and clinical site support staff can create and edit tickets, with various types like process or app-related issues. Ticket type, site ID and patient ID are required for additional context
- **Ticket Agents:** In addition to creating tickets, they can respond, reassign, or modify ticket status. They enjoy unrestricted ticket management.
- **Administrators:** Responsible for user management, including adding, removing, and modifying roles and permissions. This role is primarily held by FHJ's technical support staff.
- **Account Owner:** The initial system user, usually an FHJ developer. This role has administrative rights but uniquely, cannot be removed from the system.

4.3 Workflow Integration

In conventional, hybrid, and decentralized clinical trials, the support chain typically operates as follows:

1. Study patients approach clinical support staff or Clinical Research Associates (CRAs) with inquiries.
2. Site personnel respond or direct their questions to CRAs.
3. If an immediate answer isn't available, both site users and CRAs can utilize the Knowledge Base (KB), either by browsing topic folders or using the free text search field, as illustrated in Figure 1.
4. While the KB encompasses comprehensive resources like manuals, training materials, videos, and guidelines, some queries may remain unresolved. In such instances, clinical site support staff or CRAs initiate a ticket through the RADIAL helpdesk.
5. Ticket agents then take responsibility for managing these requests via the helpdesk's ticketing dashboard.

Ticket agents in the RADIAL trial's support system, adhering to the coverage plan, manage tickets through the ticketing system efficiently. They either assign tickets to themselves or to another more experienced agent to address the specific issue. Upon assignment, automated email notifications are sent to the respective agents.

Familiarity with the knowledge base content enables agents to direct users to relevant information or offer additional support. In scenarios where the knowledge base lacks the required information, agents have two options:

- discuss the issue in the weekly helpdesk scrum and RADIAL core study team meeting, or
- consult with study team members involved in protocol design, technology setup, or User Acceptance Testing (UAT). If necessary, they may also seek assistance from the technology provider, who will handle the issue in their ticketing system. Upon resolution, the third-party vendor informs the RADIAL helpdesk, ensuring proper documentation and closure of the ticket.

Ticket agents have the capability to include listed contacts as collaborators on a ticket. When agents respond to a query, their response is automatically dispatched to both the user's and collaborators' emails. Users or collaborators can conveniently respond back directly through their email. Each response triggers an automatic email notification to the agent, ensuring they are promptly informed. The ticketing dashboard facilitates seamless communication, allowing agents to view and reply to user responses. This interactive process, featuring email notifications to all parties, continues until the ticket creator's inquiries are fully resolved.

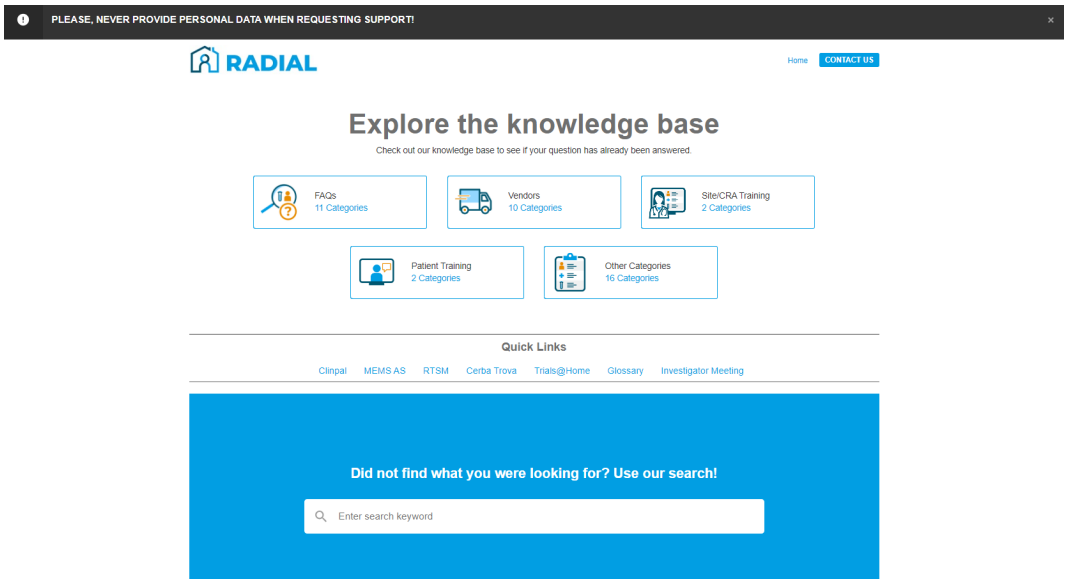

Figure 1: Start page of the RADIAL helpdesk knowledge base.

4.4 Help Desk Tickets and Issues Review and Classification

To effectively manage help desk tickets in the RADIAL study, a comprehensive approach is adopted. All help desk tickets, regardless of their status, are exported into a global issues tracker. This tracker undergoes tier review by the technology governance team, overseeing the technological aspects of RADIAL, and the Quality Assurance team, focusing on patient and data risk management. Operational teams also contribute to this process, thereby ensuring all technology-related issues are centralized in this tracker. The Governance team classifies issues into distinct categories, as outlined in Table 2. The classification determines the subsequent handling process. ”Bugs and Errors” are given high priority, potentially triggering immediate or scheduled software updates based on impact and risk analysis. ”Process-related” tickets are important and are communicated to clinical operations. ”Technical support” issues may enhance the Knowledge Base and other published materials. ”User Access and Permissions” span a range from straightforward issues, addressed with prepared responses, to complex ones necessitating detailed review or vendor escalation. Lastly, ”General Inquiries and Information” cover non-technical questions and those not fitting into other categories, ensuring a comprehensive and structured approach to ticket management.

5 OVERSIGHT

5.1 KPIs and Reports

As articulated in the work of (Bertram et al., 2010), issue trackers within the helpdesk context exhibit varied perspectives among stakeholders. Notably, project managers tend to focus on high-level summaries, while the quality assurance group categorises cases by project area or type. Enhancing existing knowledge assets necessitates the establishment of key performance indicators (KPIs). A survey conducted by (Rastogi et al., 2013) examined the significance of those indicators, soliciting ratings from two companies and distinguishing between the expectations of different roles, such as bug reporters and bug owners. Currently, foundational metrics such as the number of high-priority bugs, assigned bugs, or resolved bugs serve as the basis for RADIAL KPIs. Additionally, metrics like Priority Weighted Fixed Issues (PWFI), which not only quantify the number but also consider the priority of bugs per owner, are under consideration for analysis pending the availability of more data.

The following KPIs for Issue Tracking are actively employed in RADIAL:

- Number of Issues per day per month
- Number of Issues by Type
- Number of Issues by Status
- Number of Issues by Priority
- Number of Issues by Replies

Table 2: Issue classification like performed by Governance team.

Issue class	Description
Bugs and Errors	This category includes all issues related to software or system bugs, glitches, and errors. It covers problems that result from defects in code or applications.
Process-Related	Issues falling under this category are related to business processes, workflow, or procedures that may need improvement, clarification, or adjustment. These issues are not necessarily technical but affect how tasks are executed.
Technical Support	Technical issues that require help desk assistance or technical support team fall into this category. It includes hardware, software, network, and other technology-related problems.
User Access and Permissions	This category encompasses issues related to user access, permissions, authentication, and authorization. It includes requests for access changes and password resets.
General Inquiries and Information	For non-technical questions or general inquiries that don't fit into the other categories
Not relevant for RADIAL	Tickets not related to RADIAL

- Number of Issues by Agent
- Average Age of Issue

The process for generating those KPIs can be described into three phases which are shown in Figure 2.

Phase 1: Export data from the Issue Tracking Database. The initial step involves extracting data from the relational SQL database to create a spreadsheet, facilitating further processing for reporting purposes. Variables such as ID, status, priority, type, replies, last reply, issue age, and agent-customer associations are included.

Phase 2: Development of a Python Web application for KPIs. Subsequently, a Python Dash web application was designed to transform the spreadsheet into a comprehensible report of KPIs. This phase also entails additional preprocessing including the calculation of the average issue age and replies.

Phase 3: Expansion of the Web Application for the Knowledge Base. In this phase, the existing application is expanded to incorporate top search keywords for the current month as well as for all-time. This augmentation aims to identify prevalent issues and contribute to a more robust understanding of recurring problems.

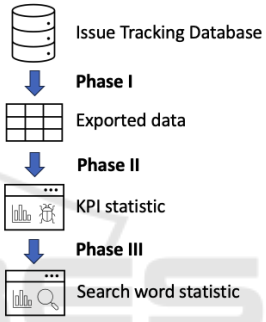

Figure 2: Phases for generating statistics of the RADIAL Issue Tracking System and the Knowledge Base.

6 CONCLUSIONS

DCTs offer several advantages over conventional trials, including reduced patient travel burden, enhanced study accessibility, and the potential for less biased and more diverse cohorts by accessing clinical studies globally. However, designing studies with remote and virtual components, such as telemedicine and mobile health devices, poses challenges. Ensuring technological stability and user self-sufficiency is crucial. Additionally, effective communication is required among stakeholders from different sites and countries, including site members and CRAs, while managing various technology providers with different service level agreements and helpdesk availabilities.

We introduced a system for the RADIAL study to address these challenges, comprising a helpdesk ticketing system for multiple stakeholders and a Wiki-like knowledge base documenting technology usage, study procedures, training materials, and FAQs.

The system is currently undergoing testing and evaluation, with additional results and insights to be published. While supporting the RADIAL study, the system facilitates clear process linking between study personnel and different technology providers. However, it has been observed that situations demanding immediate support, such as direct patient phone interactions, may encounter challenges due to

the extended communication chain involving multiple stakeholders.

The helpdesk is restricted to a limited number of users and will be enhanced in the future to increase its scalability. Caching mechanisms and daily server snapshots for backup purposes are currently being implemented to speed up the user experience. If the helpdesk experiences performance issues over time, vertical scaling can be employed to boost the existing capabilities (e.g. CPU, RAM) of the server. In the future, the helpdesk will evolve by implementing load balancing strategies across multiple servers. This will efficiently distribute incoming requests, balancing the network load and ensuring high availability by utilizing multiple servers in case of a server failure.

Despite challenges, documenting various issues during the study for quality control and risk management is essential. The implemented system allows for the collection and processing of technical bugs, process-related issues, and facilitates updates like new software releases.

Furthermore, the KB extends beyond the RADIAL study and could potentially benefit similar studies in the future. Patient access to the KB, currently unavailable, could empower patients, aligning with the trend of patient engagement. As Language Model technologies like ChatGPT emerge, the KB may serve as a domain-specific knowledge repository, enabling the training of LLMs for helpdesk chatbots. This advancement could provide more specific and straightforward support, eliminating the need for users to search diverse documents themselves.

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DISCLAIMER

The research leading to these results was conducted as part of the Trials@Home consortium. This paper only reflects the personal view of the stated authors and neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained herein.

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