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Optimizing the Use of Electronic Data Sources in Clinical Trials: The Landscape, Part 1

Ed Kellar, MS[1], Susan M. Bornstein, MPH[2], Aleny Caban, BS[1], Catherine Célingant, MA[2], Michelle Crouthamel, MS[3], Chrissy Johnson, MS[4], Patricia A. McIntire, BSc[5], Kenneth R. Milstead, MS[6], Jaclyn K. Patterson, BS[7], and Brett Wilson, BSP[8]

Abstract

Background: TransCelerate BioPharma has created the eSource Initiative with the intent to facilitate the industry's movement toward optimal usage of electronic data sources. Although guidance and standards have been in place for some time, data collection methods and technology have not been utilized to their fullest capability, and transcription between electronic systems continues to be the norm. *Methods:* The TransCelerate approach for the eSource Initiative is to understand the current landscape and highlight factors that are influencing the adoption of new technologies. As a preliminary step in this process, TransCelerate surveyed member companies regarding eSource usage and barriers. *Results:* Literature review, stakeholder engagement, and the member survey have provided insight into the current landscape, which will help TransCelerate to develop proposals for best practices for industry utilization of electronic data collection tools and methods to benefit all stakeholders. *Conclusions:* Based on survey results, companies generally have taken steps to leverage current eSource technologies and prepare for optimal utilization of electronic data sources. The TransCelerate eSource Initiative will continue to evaluate the technology, regulatory, standards, and health care landscape to support the goal of improving global clinical science and global clinical trial execution. Forthcoming publications will focus on technology landscape, future vision, and demonstration projects.

Keywords

TransCelerate, eSource, direct data capture, electronic data capture (EDC), electronic health record (eHR)

Introduction

There has been an evolving need endorsed by regulatory agencies to modernize and streamline the way sponsors and other stakeholders collect data in clinical trials.[1] In the past decades, technologies have disrupted multiple industries outside the pharmaceutical industry, including music,[2] publishing,[3] taxi,[4] and banking.[5] These industries have advanced rapidly, particularly in the areas of data collection and in the way people interface with technology; however, similar advances in the pharmaceutical industry to embrace electronic solutions for source data have been slow.

In 2013, the eSource guidance published by the United States Food and Drug Administration (US FDA)[1] clearly stated that the aims of electronic source data (eSource) should include

- eliminating unnecessary duplication of data;
- reducing the possibility for transcription errors;
- encouraging entering source data during a subject's visit, where appropriate;

[1] Development Operations, Data Science. Astellas Pharma Global Development Inc, Northbrook, IL, USA
[2] Clinical Sciences & Operations, Pfizer Inc, Groton, CT, USA
[3] Clinical Innovation & Digital Platforms, GlaxoSmithKline, Collegeville, PA, USA
[4] Operations Center of Excellence, Clinical Trial Solutions, Pfizer Inc, Groton, CT, USA
[5] Global Product Development, Pfizer Clinical Research Units, Pfizer Inc, New York, NY, USA
[6] Kinapse Inc, New York, NY, USA
[7] Early Development Global Data Management & Standards, Merck & Co Inc, Kenilworth, NJ, USA
[8] Global Clinical Operations, Bristol-Myers Squibb, Princeton, NJ, USA

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Corresponding Author:
Ed Kellar, MS, Astellas Pharma Global Development Inc, 1 Astellas Way, N-3-205, Northbrook, IL 60062, USA.
Email: Ed.Kellar@astellas.com

- eliminating transcription of source data prior to entry into an electronic case report form (eCRF);
- facilitating remote monitoring of data;
- promoting real-time access for data review; and
- facilitating the collection of accurate and complete data.

If the ultimate goal is to ensure that people have access to the safe and effective medicines they need, certainly part of this goal should be to consider how the industry uses technology to build the supporting evidence for those medicines. Appropriately utilizing eSource can have multiple benefits for stakeholders, including but not limited to the following:

- reducing unnecessary human intervention with data,
- increasing data integrity and quality,
- enabling more rapid identification of safety and operational signals,
- ensuring data security and privacy,
- enabling innovative uses of the data, and
- supporting the stated FDA goal[6] of a fully electronic review environment.

Our problem is the following: The pharmaceutical industry remains slow to widely adopt eSource despite health authority guidance, existence of relevant data standards, and technology advancements to enable inclusion of more modern approaches to electronic health record (eHR) systems. Reasons for this may not be clear, but the maturity of technology, change management needs with multiple stakeholder groups, and concerns over the acceptability of the data for primary endpoints have likely impacted the use cases for eSource. As a result, much of the exploratory work done thus far by various pharmaceutical companies has been primarily to build internal competency. It is important to recognize that such a fragmented industry approach will likely generate weak and ambiguous evidence for the utility and value of eSource.

To reduce or address the problem, the TransCelerate eSource Initiative, which launched in January 2016, aims to facilitate the understanding of the eSource landscape and the optimal use of electronic data sources in the industry to improve global clinical science and global clinical trial execution for stakeholders including patients, sites, and sponsors. The eSource Initiative aligns well with other TransCelerate initiatives that are intended to help modernize trial execution and ways in which patients participate in clinical trials.

For the purposes of the TransCelerate eSource Initiative and the content of this paper, the US FDA definition of eSource data was adopted: ''data initially recorded in electronic format.''[1] The FDA has noted that eSource data ''can include information in original records and certified copies of original records of clinical findings, observations, or other activities captured prior to or during a clinical investigation used for reconstructing and evaluating the investigation.''[1]

Substantial stakeholder engagement will be required to fully realize this transition to more widespread use of eSource, but before the industry can begin a transition to eSource in any meaningful way, it is necessary to baseline where the industry is today. A preliminary step in our approach for the eSource Initiative was to assess the current landscape. We conducted a blinded survey of member companies about their experiences with eSource and what they are already doing to transition to eSource tools and processes. The survey results have enabled TransCelerate to more efficiently and effectively compile and review existing literature concerning eSource usage in clinical trials and to engage with other stakeholders regarding the benefits and barriers to eSource. We will identify significant changes that may be needed or desirable for the industry to transition to eSource technologies and propose ways to manage that transition. This landscape assessment will also identify opportunities for projects designed to demonstrate how to successfully utilize electronic data collection methods and tools. This sponsor landscape assessment will establish a starting point for our future discussions on the topic of eSource.

Methods

For this initial landscape assessment, TransCelerate collected data through member companies (working group discussions and a survey), literature review, and engagement with selected external stakeholders. This paper reports on the results obtained through the member survey.

Working Group Activities and Discussions

In order to leverage the knowledge and experience of our team of experts from member companies, 4 working groups were created based on team classification of eSource modalities: Non–Case Report Form (CRF) Data, Direct Data Capture (DDC), Devices and Apps, and eHRs. It is recognized that there are several other ways the categories of focus could have been created and that some technologies may not neatly fit into a single category, but these categories were considered appropriate for our discussion purposes. Each working group conducted extensive discussion and research into their assigned subject areas. Table 1 depicts the scope of each of the working groups.

The working groups also considered the importance of standards when attempting to integrate data from various modalities. For the purposes of this discussion, ''standards'' includes the use of clinical data standards (eg, Clinical Data Interchange Standards Consortium [CDISC], Health Level Seven International [HL7]), process standardization, and standard methods of data collection into systems (eg, eHR) that would mimic clinical research modules.

Survey

A survey was created for TransCelerate member companies to collect information regarding current global eSource utilization within their companies, capabilities, planned future uses, value proposition, and unmet needs. Surveys were distributed to 17 member companies through points of contact. Survey

Table 1. Scope of eSource Working Groups.

Working Group	Description
Non-CRF Data	Includes collection and transfer of data in electronic format from internal sponsor sources (eg, specialty laboratories) or external vendors (eg, laboratory results, imaging, ECG, randomization, drug accountability) into clinical research data repositories/warehouses without entering the data on a CRF.
Direct Data Capture	Includes direct entry of clinical data by site staff into a mobile application or EDC system.
Devices and Apps	Covers collection and management of clinical data from nonsite personnel (subjects, participants, and caregivers) using mobile devices including smartphone or tablet applications (eg, electronic clinical outcome assessment), wearables, and sensors (eg, glucose monitor, smart pill, remote chemistry, ambient sensors).
Electronic Health Records	Covers collection of clinical data for use in clinical research from site electronic health record systems.

Abbreviations: CRF, case report form; ECG, electrocardiography; EDC, electronic data capture.

responses were collected by a third party, and data were aggregated for analysis on an anonymous basis.

Literature Review

A literature review was conducted using PubMed with keywords and database-specific terms identified by the members of the eSource Initiative team and by collection of relevant regulatory guidance documents. The literature review used the following search terms and appropriate synonyms: *electronic case report form*, *electronic source data*, *digital health record*, *direct data capture*, *EDC*, *remote data capture*, *paperless trial*, *electronic clinical outcome assessment*, *electronic patient reported outcome* (*ePRO*), *electronic diary*, *apps*, *patient engagement*, *compliance*, *adherence*, *medical application*, *electronic data transfer*, *data mapping*, *eHR*, and *meaningful use*.

Abstracts were reviewed for relevance, and selected full-text articles were reviewed. Relevance criteria used included recent publication (ie, within the past 5 years). Materials specific to a particular project (eg, case studies) were not considered unless they pertained to landmark studies. The literature review focused on articles of general applicability to eSource rather than detailed focus on a specific topic area. The literature review and company survey completion were performed in parallel, and both the literature review search terms and the survey questions were based on prior team discussions and research.

Stakeholder Discussion

In order to maximize some of the lessons learned through survey and literature review, feedback was sought from regulatory authorities on the results of this assessment as well as the overall approach of the TransCelerate eSource Initiative. For this paper, discussions were also conducted with data standards organizations (CDISC and HL7) to discuss the eSource-related activities and perspectives of each group. Written feedback was obtained from the FDA, and verbal comments were received from the European Medicines Agency (EMA) related to the approach. The next step of this landscape assessment will include a focus on technology capabilities with input from technology providers.

Results

Survey

Of the 17 companies that received the survey, 13 companies responded. In some cases, not all questions were answered, but all collected data were compiled.

Non-CRF Data

Electronic transfer of such data was widespread, and the majority of responding companies have established policies and practices to receive, process, and clean the data types that they use most frequently in their studies (eg, standard file formats, standard operating procedures [SOPs], use of data standards). Planned use of various types of non-CRF data by member companies is presented in Figure 1.

Survey responses showed several barriers or challenges faced when using non-CRF data. There were common themes in the types of barriers companies reported in the survey. Non-CRF data are the most mature modality of eSource; however, many challenges shared by sponsors, vendors, and technology providers still exist. These include use of standards, delivery of expected data file formats, personnel training, uptake of new technology, and adherence to timelines. Although these data are collected in electronic format, sponsors and vendors still use nonautomated processes (eg, manual file transfers, study-specific data transfer agreements, data loading) to prepare the data for submission. There is a reliance on manual data mapping and ''batch'' data loads, instead of using semantically interoperable and continuous data interchange and monitoring.

Survey respondents reported several advantages of utilizing non-CRF data. The information collected is reported in Table 2. Other (free-text) responses indicated that use of non-CRF data may result in resource savings at the investigative sites, better protocol compliance, and raw data files that provide additional data for sponsor exploratory analyses for future protocol improvement.

Survey responses appear to reflect a consensus about practices that will facilitate eSource uptake for non-CRF data in clinical studies. Table 3 shows company opinions concerning best practices for handling non-CRF data. Other common practices included working closely with vendors and site information technology (IT) staff.

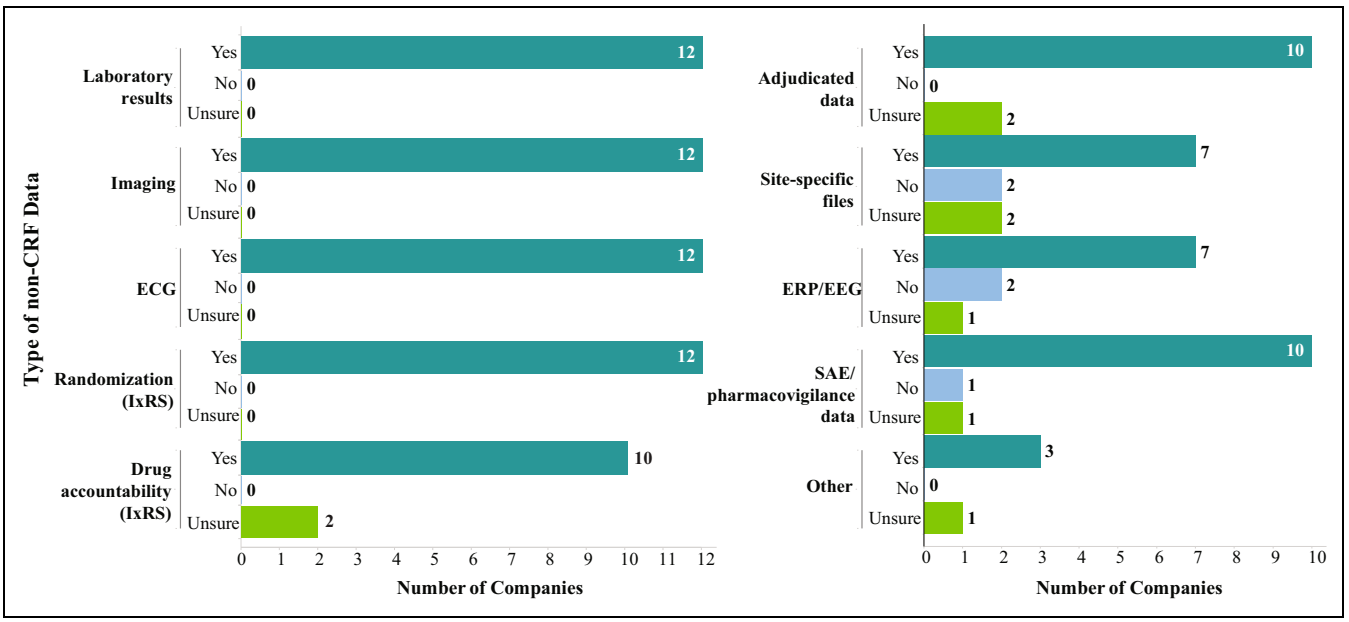

Figure 1. Planned use of non-CRF data by type of data. Abbreviations: CRF, case report form; ECG, electrocardiography; ERP/EEG, event-related potential/electroencephalography; IxRS, interactive response technology; SAE, serious adverse event.

Table 2. Advantages of Utilizing Non-CRF Data.

	No. of Responses (%[a])
Less SDV	11 (91.7)
Higher quality data	10 (83.3)
Predefined format of incoming data	9 (75.0)
Resource savings	7 (58.3)
Timeline reduction	5 (41.7)
System platform flexibility	3 (25.0)
Other responses	3 (25.0)

Abbreviations: CRF, case report form; SDV, source data verification.
[a]Percentages are based on n = 12 responses.

Table 3. Best Practices for Handling Non-CRF Data.

	No. of Responses (%[a])
Standard file specifications	12 (100.0)
Standard data handling processes	12 (100.0)
Secure method for file transfer	11 (91.7)
Test transfer file	11 (91.7)
Defined data flow process	11 (91.7)
User acceptance testing	9 (75.0)

Abbreviation: CRF, case report form.
[a]Percentages are based on n = 12 responses.

Current standard data specifications and practices used by responding companies for non-CRF data varied depending on the data type, as displayed in Table 4. Over 70% of responding companies reported using external data specifications for laboratory results (80%), imaging (80%), electrocardiography (ECG; 72.7%), randomization (77.8%), and adjudicated data (71.4%). Responding companies also noted the use of company-specific internal data specifications (including internal company CDISC interpretations), SOPs, standard documents and report templates, and vendor native file formats.

Direct Data Capture

Electronic data capture (EDC) systems have become commonplace in clinical research in the past decade, largely replacing use of paper CRFs. Consequently, one method of adopting eSource is to use existing EDC systems for data collection without first creating separate source documents. We surveyed member companies regarding their current use of EDC systems. All 13 responding companies reported using one or more EDC systems. In cases where a company reported using more than one EDC system, respondents noted that the decision to use a system for a given study was based on certain factors. Study phase (7 of 11; 63.6%) and sourcing model (5 of 11; 45.5%) were the most frequently reported decision factors. Other reported factors included study size, country, and therapeutic area (TA).

Information was collected on previous or current use of one or more EDC or tablet systems as DDC eSource (Figure 2) and investigation of DDC eSource capabilities for future use (Figure 3).

Three of 10 responding companies indicated definite plans for implementing DDC eSource, 4 companies reported that they were considering DDC eSource, and 1 company indicated that they were not currently considering such use. Additional details are presented in Figures 4 and 5.

Seven responding companies provided information regarding the study phases in which they are planning to implement DDC eSource (Figure 6). Ten unique TAs were reported by 6 companies; the number of TAs under consideration by an

Table 4. Current Process Standardization Used for Non-CRF Data.[a]

	Laboratory Results (n = 10)	Imaging (n = 10)	ECG (n = 11)	Randomization (IxRS) (n = 9)	Drug Accountability (IxRS) (n = 7)	Adjudicated Data (n = 7)	ERP/ EEG (n = 5)	SAE/ Pharmacovigilance Data (n = 6)
External data specifications	8 (80.0)	8 (80.0)	8 (72.7)	7 (77.8)	4 (57.1)	5 (71.4)	2 (40.0)	3 (50.0)
Internal data specifications	6 (60.0)	6 (60.0)	6 (54.5)	8 (88.9)	5 (71.4)	3 (42.9)	1 (20.0)	4 (66.7)
Standard process/SOPs	5 (50.0)	5 (50.0)	5 (45.5)	6 (66.7)	3 (42.9)	4 (57.1)	2 (40.0)	4 (66.7)
Standard documents	5 (50.0)	5 (50.0)	6 (54.5)	5 (55.6)	3 (42.9)	3 (42.9)	1 (20.0)	3 (50.0)
Standard report templates	2 (20.0)	2 (20.0)	3 (27.3)	4 (44.4)	3 (42.9)	2 (28.6)	1 (20.0)	2 (33.3)
Other	3 (30.0)	2 (20.0)	1 (9.1)	0 (0.0)	1 (14.3)	1 (14.3)	3 (60.0)	1 (16.7)

Abbreviations: CRF, case report form; ECG, electrocardiography; ERP/EEG, event-related potential/electroencephalography; IxRS, interactive response technology; SAE, serious adverse event; SOP, standard operating procedure.
Values are presented as number of responses (%). Percentages are based on the total subsample size indicated in each column header.

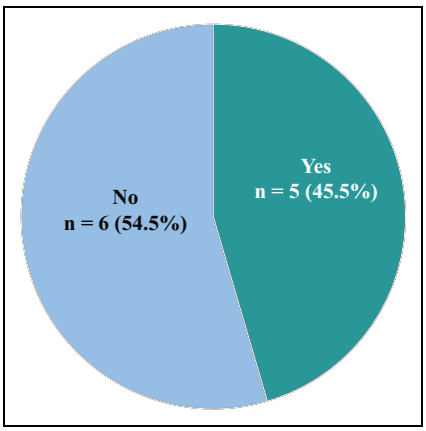

Figure 2. Previous or current use of one or more EDC or tablet systems as DDC eSource. The number of systems used by each company ranged from 1 to 5; overall, companies reported use of 9 unique EDC systems.

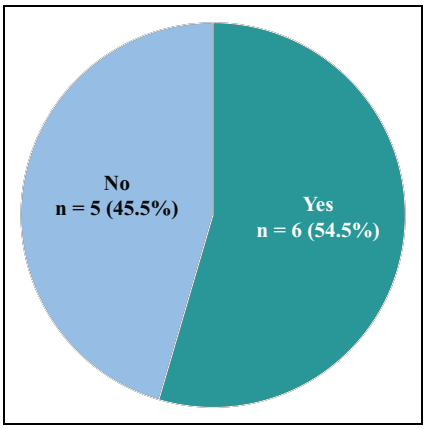

Figure 3. Investigated DDC eSource capabilities for EDC or tablet systems for future use. The number of systems assessed ranged from 1 to 4; overall, investigation of 7 unique systems were reported.

individual company ranged from 1 to 6. Oncology, neuroscience, and rare disease were the most commonly mentioned TAs. One additional company reported that TA is not yet a selection criterion for DDC usage, while another company noted that each TA has unique DDC considerations that require evaluation.

Seven companies with experience using DDC systems reported on the significant challenges they experienced that would affect future decisions (Table 5). Challenges noted by over 50% of the respondents include site training (71.4%), site infrastructure (71.4%), time-consuming study start-up (57.1%), and expense of the software or platform used (57.1%). Other free-text comments included device management logistics (both delivery and replacement).

Devices and Apps

Devices and apps potentially enable capture of real-time patient data in an unprecedented way (ie, with high variety,

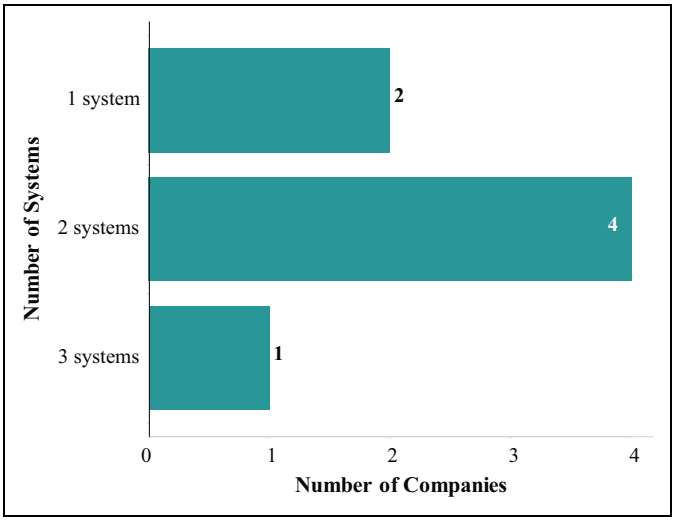

Figure 4. DDC future use companies: number of systems evaluated. Evaluation of 8 unique systems were reported.

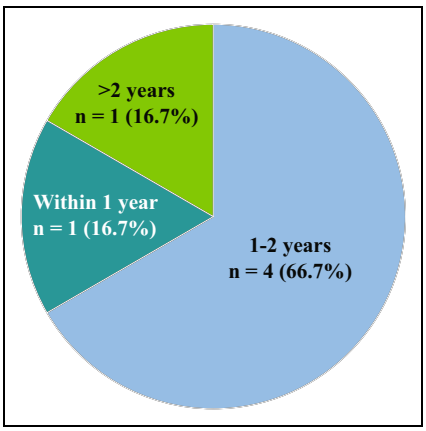

Figure 5. DDC planned implementation time frame (n = 6 companies).

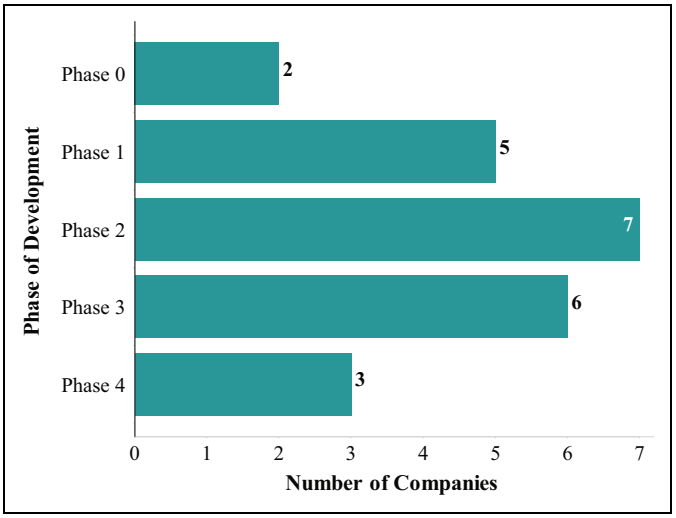

Figure 6. Plans to implement DDC eSource: study phases. Ten unique therapeutic areas were reported by 6 companies.

volume, and velocity at a low cost). The area of devices and apps is an active one in clinical research, as our PubMed search yielded over 100 published case studies within the past 5 years. Member companies have disclosed experiences of conducting pilot studies to collect data from trial participants using devices and apps; however, because of factors such as organizational silos, willingness to share information, and/or lack of central coordination/tracking, we are unable to present a summary of previous and current activities among member companies in this particular category.

For survey purposes, devices and apps were classified according to the following categories:

- electronic clinical outcome assessment (eCOA) apps,
- eConsent apps,
- patient engagement apps (eg, disease education, exercise, medication),
- class I/II medical apps (eg, diagnosis, dose calculation),
- class I/II medical devices (eg, ECG, glucometer, blood pressure),
- consumer-grade well-being devices (eg, actigraphy), and
- medication adherence tracking devices (eg, smart bottle).

Table 5. Challenges Experienced With DDC Usage.

	No. of Responses (%[a])
System not user friendly	2 (28.6)
Logistics	
Study start-up too time consuming	4 (57.1)
Study conduct too time consuming	1 (14.3)
Study close-out too time consuming	1 (14.3)
Expense	
Of software/platform	4 (57.1)
Of devices required (eg, tablets)	3 (42.9)
Minimal cost savings realized	2 (28.6)
Frequent software upgrades	1 (14.3)
Regulatory concerns	2 (28.6)
Site training	5 (71.4)
Sponsor training	1 (14.3)
Site infrastructure	5 (71.4)
Site resistance	3 (42.9)
System validation	1 (14.3)
Sponsor infrastructure	0 (0.0)
Business process impact	
Data management	1 (14.3)
Monitoring	2 (28.6)
EDC form design	0 (0.0)
Other	2 (28.6)

Abbreviations: DDC, direct data capture; EDC, electronic data capture.
[a]Percentages are based on n = 7 responses.

Plans for future use of devices and apps by responding companies are reported in Figure 7. For all listed technologies other than medication adherence tracking devices, at least 60% of the responding companies expect to implement these technologies within 1 year.

Figures 8 and 9 show the top obstacles encountered by respondents in their efforts to successfully implement devices and apps in clinical trials. While challenges differed for the various categories of devices and apps, frequently noted obstacles included

- lack of organizational alignment,
- regulatory challenges and uncertainties,
- site and sponsor resource challenges,
- cost/budget concerns, and
- infrastructure challenges.

Responses to the most important factors related to successful implementation of devices and apps based on the companies' experiences in studies conducted to date are shown in Figures 10 and 11. Frequently noted factors that support implementation included

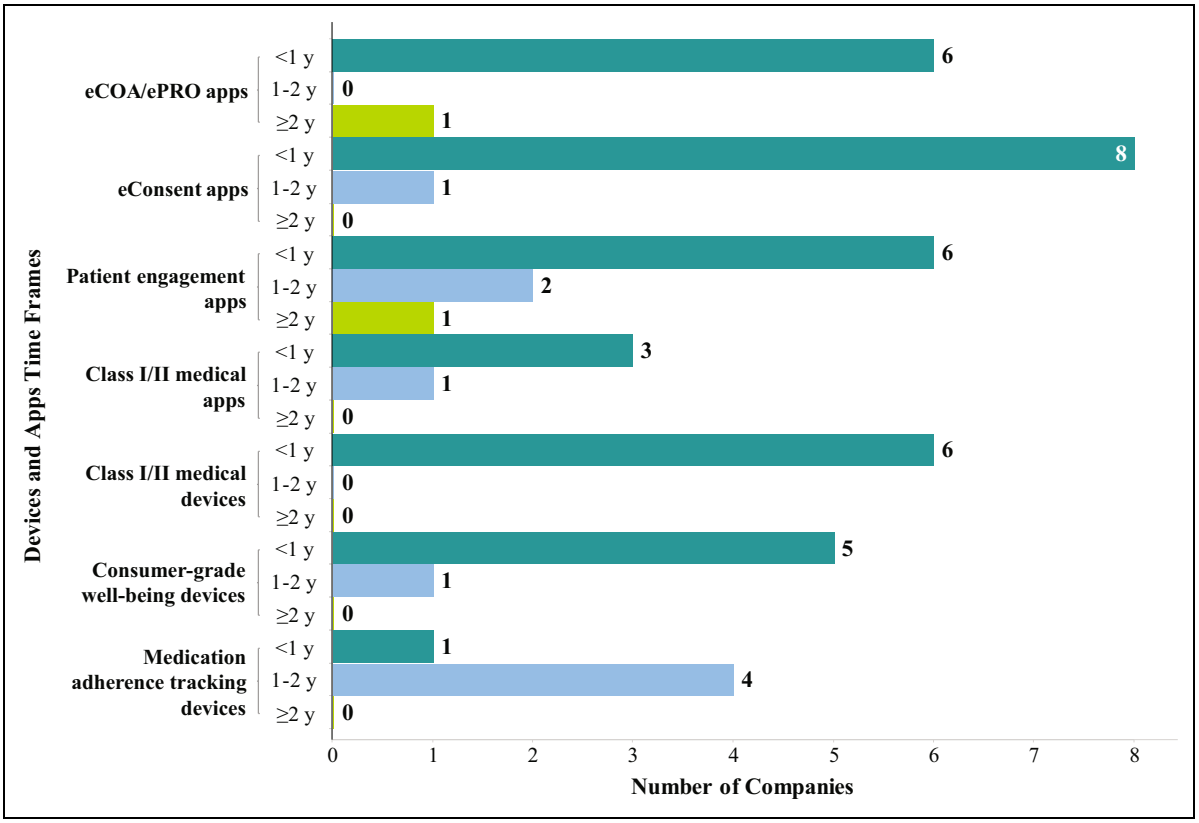

Figure 7. Reported time frames for future use of devices and apps.

- proper organizational structure and support,
- clear regulatory guidelines,
- management support,
- site resource availability, and
- availability of internal sponsor expertise.

Current standard data specifications and practices used by responding companies for devices and apps data varied depending on the data type. Use of external data specifications was less common than reported for non-CRF data, but this is likely due to the lack of widely accepted standards for some of the indicated data types. Companies noted the use of internal data specifications, SOPs, and standard documents and report templates to promote consistent data handling.

Electronic Health Records

Ongoing efforts in the health care industry to enhance patient safety, patient outcomes, and operational efficiency, coupled with global government-led eHealth initiatives[7] have made eHR systems increasingly pervasive in clinical practices. This creates an opportunity to leverage the data contained within these eHR systems to support clinical research activities.

When asked whether they had an overarching strategy to utilize eHR systems for eSource to enable clinical trials, 5 of 10 (50%) responding companies stated that they had a strategy, while 5 of 10 (50%) stated that they did not. Two companies (one with a policy and one without) noted that they were using pilot studies to inform and define such a strategy. Seven companies provided a timeline for implementing an eHR strategy, as denoted in Figure 12. Companies expressed plans to utilize data from eHR systems in trials across all clinical development phases.

When considering eHR use, the direction of dataflow should also be considered. The continuity of care and completeness of health records could be facilitated by a bidirectional data flow between eHR and sponsor systems to ensure comprehensive medical records for participating subjects. When asked about the planned transfer of data between eHR and sponsor systems, 5 of 8 (62.5%) companies stated that they plan unidirectional flow from eHR to sponsor databases, while 3 of 8 (37.5%) plan bidirectional data flow. One company (12.5%) stated that this decision was unclear at this point in time.

Responding companies foresee a need to accommodate a wide range of eHR systems that may be in use at sites selected for a particular study. As such, the responding companies noted plans to work with a variety of eHR systems and commented that eHR systems may vary based on TA (eg, use of oncology-specific eHR systems).

Of the 10 responding companies, 2 (20%) responded that they have already exchanged data to/from eHR systems in a clinical study, while 8 (80%) stated that they have not yet done so. For both companies where eHR data have been exchanged,

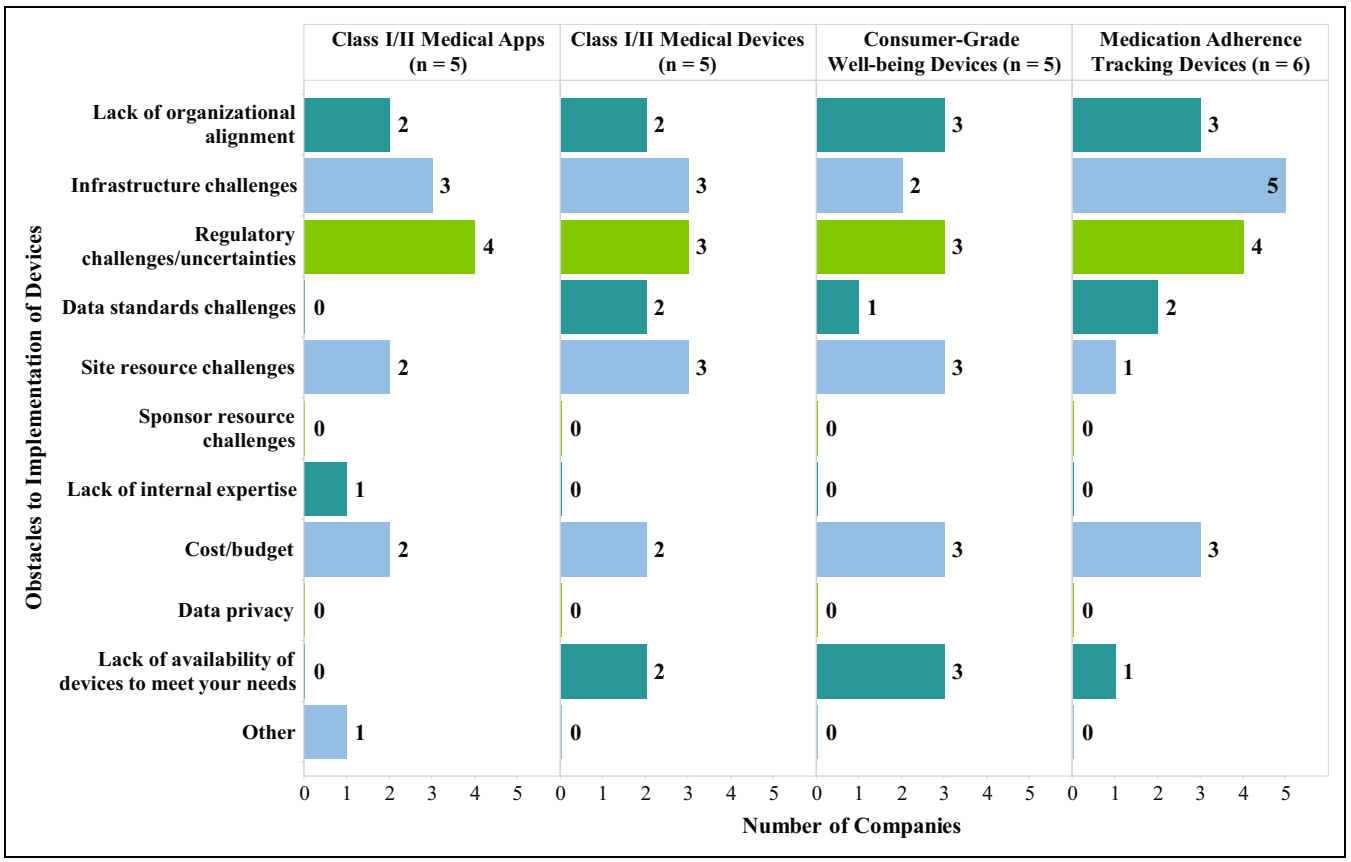

Figure 8. Devices and Apps (Part 1): Top obstacles to successful implementation in clinical studies.

the data were not used in support of a regulatory submission, but one company noted that the data were used to fulfill a regulatory approval pharmacovigilance obligation. Of the 8 companies that responded that they have not yet exchanged data to/from eHR systems in a clinical study, 7 provided information regarding their future plans. Of these 7 companies, 6 (85.7%) have plans to exchange data to/from an eHR with 3 (50%) planning to do so within 1 year, 1 (16.7%) within 1 to 2 years, and 2 (33.3%) more than 2 years from present. One company (14.3%) stated that they have no such plans at present.

While none of the 10 responding companies have developed detailed policies and procedures to support use of eHR data, 1 company (12.5%) plans to develop such procedures within the next year, 3 (37.5%) plan to develop within 1 to 2 years, 4 (50%) plan to develop more than 2 years from present, and 2 have no plans to develop.

While the diversity of information contained within eHR systems can accommodate many potential uses, clinical research uses may be generally classified into the areas of study feasibility and design, site and subject recruitment, and data collection.

Top obstacles to utilization of eHRs in clinical research (cited by more than 30% of companies) were reported as

- no continuum of regulatory requirements between clinical research and health care;
- different data standards between clinical research and health care;
- unreliable, nonstandard, nonvalidated, or outdated eHR systems;
- concerns with interoperability;
- uneven adoption of eHRs across geographical regions; and
- concerns with data quality.

There was considerable consensus on the importance of standards for utilization of eHR systems in clinical research (Figure 13). Although the data illustrate some disagreement to a series of questions related to use of standards, analysis of the comments from those who disagreed indicates the importance of data standards but also reflects the opinion that lack of the existence or use of data standards should not delay using eHR data to support clinical trials.

Results From Literature Review

The US FDA has issued a number of guidance documents relevant to eSource. In September 2013, FDA released a guidance for industry titled "Electronic Source Data in Clinical Investigations."[1] In May 2016, FDA released a draft guidance, "Use of Electronic Health Record Data in Clinical

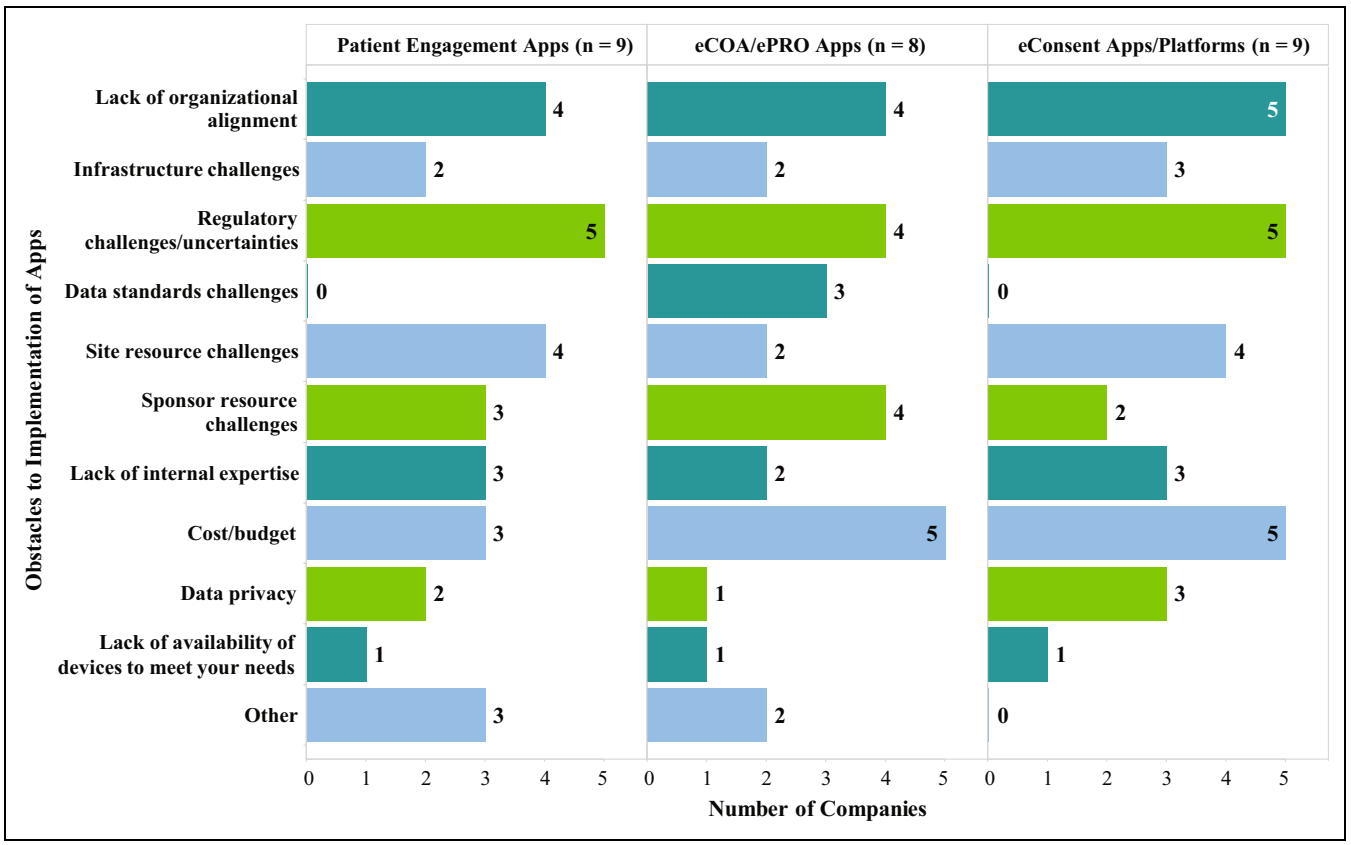

Figure 9. Devices and Apps (Part 2): Top obstacles to successful implementation in clinical studies.

Investigations: Guidance for Industry."[8] Other relevant FDA documents include "Computerized Systems Used in Clinical Investigations"[9] (May 2007) and FDA regulations on electronic records and electronic signatures (21 CFR Part 11).[10] In addition, the EMA released the "Reflection Paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection Tools and Clinical Trials"[11] in June 2010, and the Medicines & Healthcare products Regulatory Agency (MHRA) released its "MHRA Position Statement and Guidance: Electronic Health Records"[12] in September 2015.

There have been a number of recent industry initiatives relevant to eSource. In 2006, the eClinical Forum and the Pharmaceutical Research and Manufacturers of America (PhRMA) EDC/eSource Taskforce generated a discussion document titled "The Future Vision of Electronic Health Records as eSource for Clinical Research."[13] The eClinical Forum released the eSource Readiness Assessment in 2015 to assist sponsors in evaluating the readiness of clinical sites for use of their eHR systems for clinical research purposes. The Society for Clinical Data Management has produced 2 white papers on this subject: "eSource Implementation in Clinical Research: A Data Management Perspective"[14] in June 2014 and "eSource in Clinical Research: Use of Mobile Health Technology—A Data Management Perspective" in September 2016.[15] In addition, both CDISC[16] and HL7[17] have established working groups related to eSource. The US FDA and TransCelerate member companies are participating in both of these efforts.

The US FDA issued a call in June 2015 for demonstration projects to "test the capability and evaluate performance of using an end-to-end eHR-to-EDC single-point data capture approach, using established data and implementation standards in a regulated clinical research environment" and published a list of responses in the Federal Register in December 2015.[18] CDISC has also issued a call for demonstration projects, and the TransCelerate eSource team also plans to conduct demonstration projects. TransCelerate plans to conduct additional demonstration projects to complement the demonstration projects presented by other organizations.

Literature review resulted in numerous articles concerning eSource modalities, but the current focus was necessarily limited to articles that were general in nature. Two sets of articles are presented: Table 6 discusses use of data standards in eSource, including challenges related to transfer of data between eHR systems and clinical research systems. Table 7 discusses challenges related to collection and use of eSource data including assessment of quality of eHR data and logistics of implementation of new technology in clinical research settings.

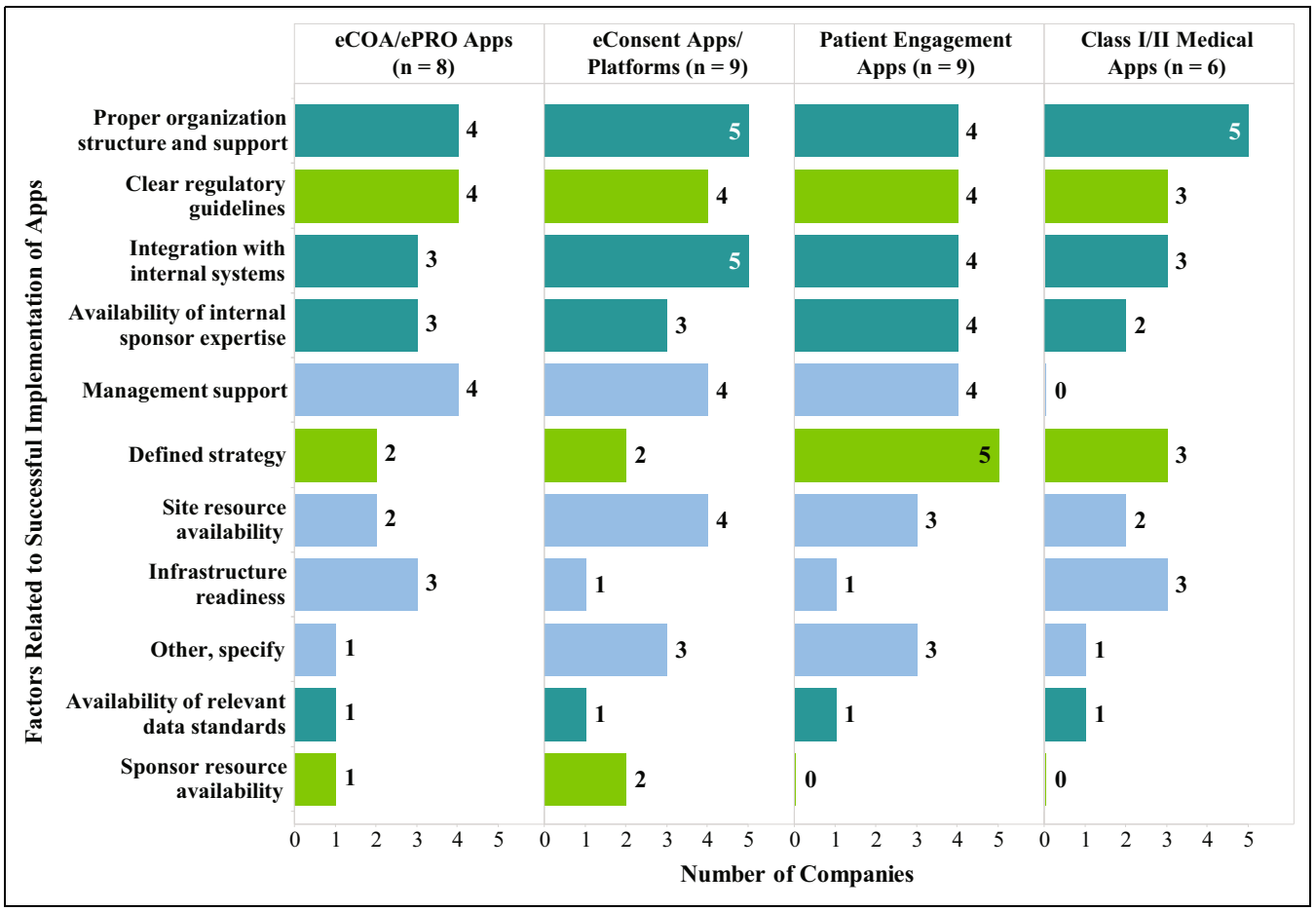

Figure 10. Apps: Most important factors related to successful implementation based on experience in conducted studies.

Discussion

Utilizing data in its original electronic format has the potential to streamline clinical research data collection, simplify the clinical research process, facilitate development of objective measurements and endpoints (potentially replacing many surrogate endpoints currently used), increase frequency and level of data collection, allow on-demand data availability, increase data quality, and enhance patient engagement with the clinical research process and/or an understanding of his/her medical condition. Although obstacles in the current landscape of eSource modalities (such as eHRs and non-CRFs) have been noted by respondents, the resolution of these stumbling blocks may lead to greater reliability with these eSource systems in future clinical trials. The awareness of similar concerns and benefits such as data quality, use of standards, and interoperability within different eSource modalities will help to create systems that provide accurate data in clinical research.

Survey results indicate that many companies have made good progress toward utilizing non-CRF data in its electronic format as well as ePRO/eCOA data. Efforts have been made to prepare for an environment to support data collection through utilization of DDC, devices and apps, as well as eHRs. There is certainly a need to continue to progress toward a goal of fully utilizing patient data from electronic sources to support clinical trial submissions. The potential to accelerate access to data can

- facilitate the use of adaptive designs as well as remote or central monitoring activities,
- enable more rapid identification of safety and efficacy signals and trends across a global footprint,
- allow resource deployment to be focused on areas of risk or concern, and
- benefit patient care by allowing physician investigators to evaluate patient data holistically and make decisions on standard of care and dosing adjustments in a more timely manner.

Non-CRF Data

According to the member company survey, non-CRF data are the most mature eSource modality. Sponsors have been receiving and submitting these data to regulatory agencies in registrational trials for more than a decade. However, the survey (Table 3) did highlight the fact that the processes member companies use to collect and handle these data still vary despite

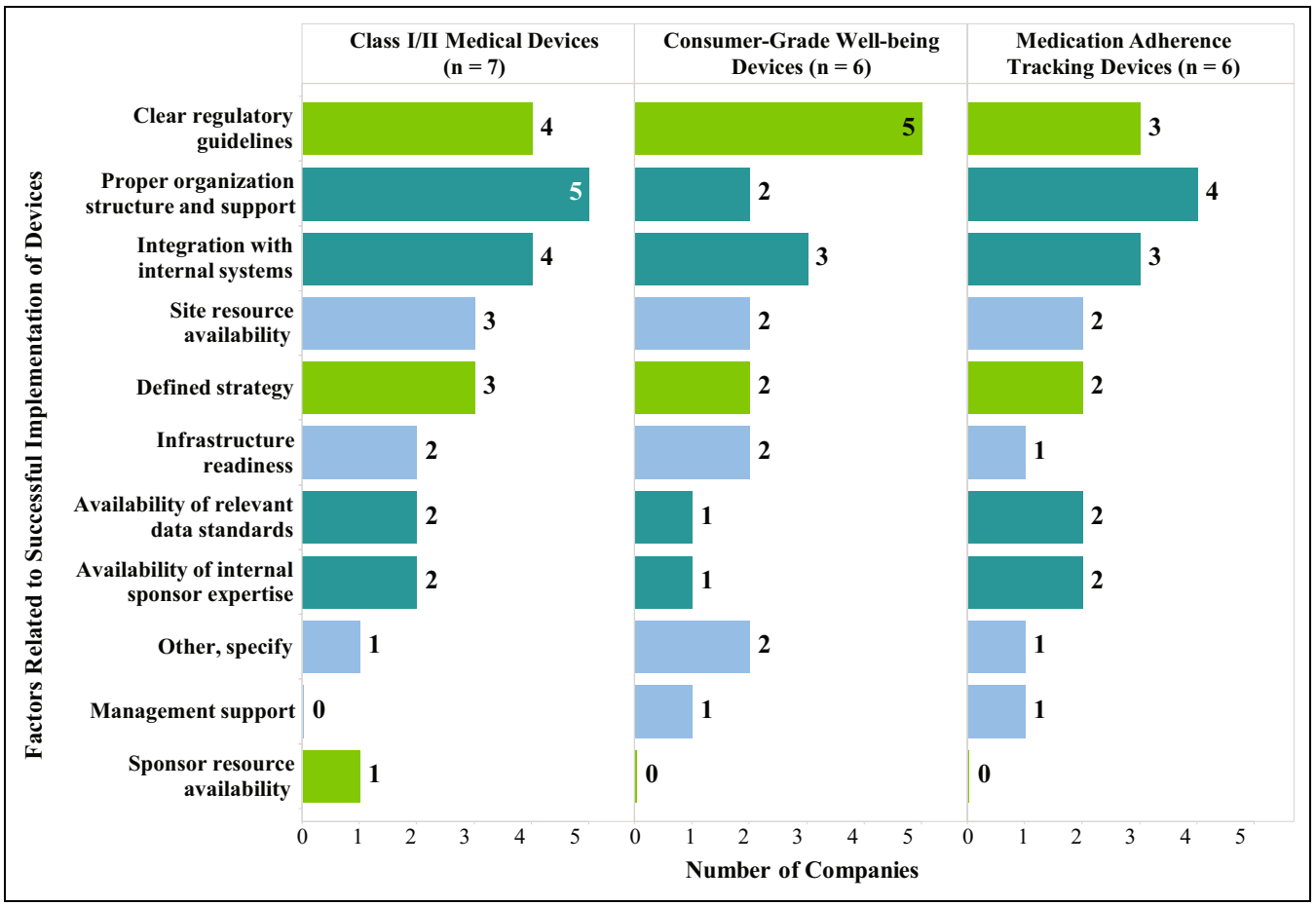

Figure 11. Devices: Most important factors related to successful implementation based on experience in conducted studies.

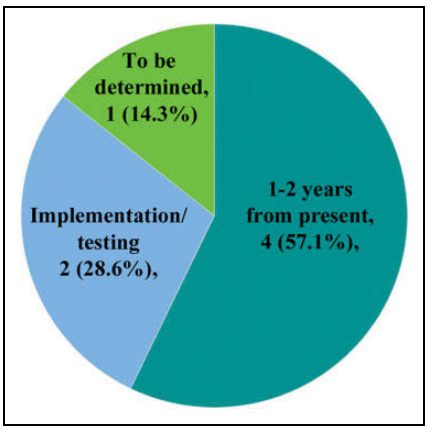

Figure 12. Planned timeline for implementing an eHR strategy.

the maturity of this modality. Additional effort is needed to align sponsors on use of existing data standards and adoption of standard processes and supporting tools and templates. Efforts to implement best practices and increase operational excellence for these familiar data types will help overcome previously discussed barriers, and may be applicable to newer, less familiar forms of eSource data.

Direct Data Capture

DDC can reduce the use of paper source documents and the need for manual data transcription. As discussed in the Results section, many responding companies have managed to transition much of their data collection from paper to electronic sources by directly transferring non-CRF data, but the prevalence of eSource DDC for other data, typically collected in EDC today, is currently uncommon within the industry. The survey tends to show that companies are investigating ways to further leverage their EDC investments to enable paper source reduction. DDC offers the opportunity to meet current requirements for data submission to regulatory authorities, provided their expectations are met. DDC systems designed with end users (eg, clinicians, nurses, pharmacists) in mind can enable efficient data collection during the subject visit, minimize disruption to existing site workflow, allow rapid investigator and sponsor data access, and minimize time spent transcribing data and checking transcription.

Devices and Apps

Devices have been used for years to measure temperature, blood pressure, ECG, and similar measures. Recently, the

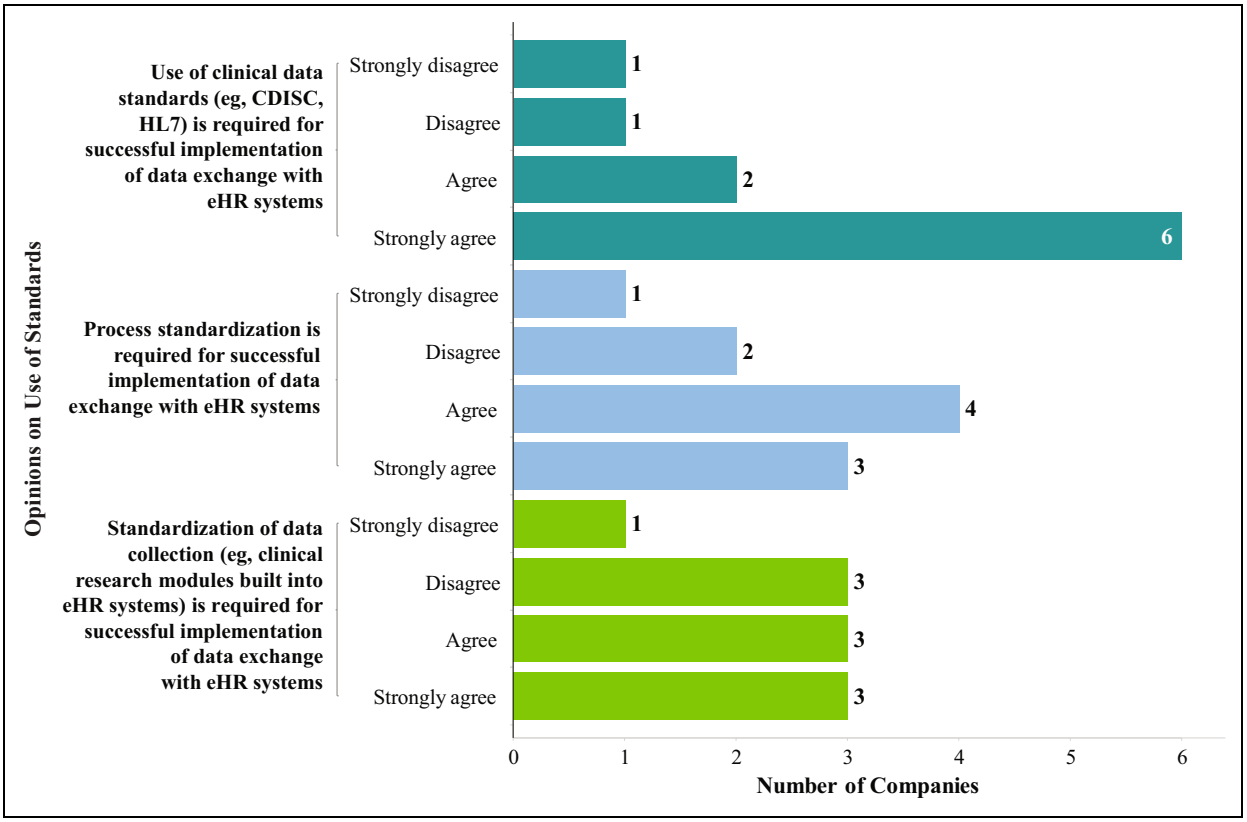

Figure 13. Opinions regarding use of standards in utilization of eHR systems in clinical research.

Table 6. Literature on Use of Data Standards in eSource (EDC, eHR, etc).

Article	Summary
De Moor et al (2015)[19]	The European Innovative Medicine Initiative (IMI) EHR4CR project has developed a platform to demonstrate how EHR data can be reused for clinical research purposes. "A central EHR4CR 'pivot terminology,' which is largely based on existing standards such as ICD10, LOINC, and SNOMED-CT, acts as the principal broker between heterogeneous terminology systems. . . . " Pilots have been conducted for two services under this initiative: protocol feasibility and patient identification and recruitment.
Dugas et al (2016)[20]	Medical Data Models (MDM) is a registered European information infrastructure. It provides a multilingual platform for exchange and discussion of data models in medicine, both for medical research and health care. The goal is to foster the development of interoperable data models to support exchange of data between systems, especially between EDC and eHR.
Gupta (2015)[21]	"During the trial period, the standards reduce the amount of queries generated, improve data quality, and reduce the time to lock the database. These standards allow the regulatory bodies to run their review-tools on the submitted data, leading to far fewer questions about the data structure and, therefore, shorter review cycles with faster approval. In addition, data standards simplify the data transfer between data providers and data receivers while the trial is ongoing." "There is a consensus that the promotion of proven global standards has a vital role to play in sustaining efficient and economic data sharing."
Dugas (2015)[22]	The feasibility of automatically converting CDISC Operational Data Model (ODM) formatted data into HL7 Clinical Document Architecture (CDA) format and vice versa was assessed. The results showed that, while it is technically possible to convert data between these formats, the transformation is "lossy" as these formats were created for different purposes and have unique structural differences which inhibit data conversion.
Koppel and Lehmann (2015)[23]	In the absence of data standards that enable data to be exchanged among eHR systems, one of the advantages of a monopolistic system is a "de facto establishment of data standards."

Abbreviations: EDC, electronic data capture; eHR, electronic health record.

Table 7. Literature on eSource challenges.

Köpcke et al (2013)[24]	Discusses results of an assessment of usability of eHR records for clinical trial recruitment support in 5 German university hospitals. Compared protocol eligibility requirements with patient eHR data. Determined percentage of required eligibility data available in eHR for the selected clinical trials.
	Structured data on patient's medication were noted as "currently almost non-existing." Best performing semantic groups in eHR were age, gender, addictive behavior, disease, symptom, sign, and organ or tissue status.
	Structured data are favored in areas for billing purposes and laboratory data.
Weiskopf and Weng (2013)[25]	Focuses on assessing the quality of data in eHRs. The authors note that the clinical research community has largely failed to develop or adopt a consistent taxonomy of data quality and that this is necessary if the reuse of clinical care data for clinical research is to become accepted practice.
	Five dimensions of data quality were identified: completeness, correctness, concordance, plausibility, and currency. Seven broad categories of data quality assessment methods are discussed: comparison with gold standards, data element agreement, data source agreement, distribution comparison, validity checks, log review, and element presence.
	Past literature references on eHR data quality are discussed.
Schick-Makaroff and Molzahn (2015)[26]	Identify issues (ethical, implementation process, and data collection) encountered in a study including tablet-based electronic capture of patient-reported outcomes (ePRO) in 2 home dialysis units.
	Four core issues are identified: technology logistics, data security, institutional and financial support, and electronic design.
	Authors discuss the strategies used to address identified issues (eg, concerns regarding potential government access to confidential patient data under data access laws).

Abbreviation: eHR, electronic health record.

world of health-related wearable devices and apps has exploded as a major component of the "Internet of Things": "the network of physical objects—devices, vehicles, buildings and other items—embedded with electronics, software, sensors, and network connectivity that enables these objects to collect and exchange data."[27] Researchers and regulators face the challenge of sorting through thousands of available devices and apps to determine which technologies are suitable for clinical research use as well as managing the resulting large variety, velocity, and volume of data collected. Since these devices are proprietary, it is also important to understand the algorithms used by vendors and the possible impact of ongoing changes to these algorithms during studies.

Despite the previously presented challenges involved with identifying and effectively using devices and apps, they hold considerable potential value for clinical research. For example, use of devices and apps (alone or in combination with other eSource modalities) could be a major component to enable remote participation by patients in clinical trials.

Along with the potential advantages, there are corresponding risks and challenges (Table 7). For example, collection of data (eg, activity levels, vital signs) using a personal fitness device could replace a diary question regarding the patient's physical activity since his/her last visit. This information is more objective than the diary data collection, but would result in a large volume of data that must be stored, processed, analyzed, and interpreted. Confirmation is needed to ensure that the device accurately collects the information reported (eg, are the reported daily steps walked actual patient mobility data, or is the device incorrectly measuring other activity such as hand motion during a conversation) and that the data and metadata (eg, date and time stamps) are reliable and accurately transmitted to the clinical research data repository.

It is important that data collected and reported in clinical research are clinically meaningful (ie, they represent a valid, clinically accepted measurement). Use of devices and apps for more direct data collection from research participants will require research into development of new valid endpoints (eg, surrogate biomarkers to indicate efficacy). Development of such reliable new endpoints will require contributions from technology, pharmaceuticals, health care, and regulators.

Electronic Health Records

Although an increasing number of clinical research sites utilize eHRs for their patient records, information from the eHR is typically transcribed by site personnel onto eCRFs in a sponsor's EDC system (and sometimes even to paper copy prior to EDC entry). This existing approach is inefficient for both sites and sponsors as it requires manual effort, and it introduces the potential for transcription error and missing data in the clinical trial database.

Direct access to eHR data offers major potential operational gains to those involved with medicine development, but considerable effort is required to prepare the continuum of patients, health care providers, eHR vendors, other clinical and research technology providers, the pharmaceutical industry, standards organizations, and regulatory authorities for this new paradigm.

The survey shows that while there is interest in the potential value of using data directly from eHRs in clinical research, there is also a significant need to better understand this area in order to fully take advantage of the advances in health care electronic systems. Several responding companies noted that

lack of standards and interoperability are major concerns. Standards organizations such as HL7 and CDISC are focused on facilitating a move to interoperability; however, there is a need for continued collaboration among regulatory agencies, technology companies, and industry to ensure that future innovations meet global needs.

Recommendations for overcoming obstacles specific to eHR adoption include but are not limited to the following:

- demonstrate the ability to protect data and to ensure the quality of eHR data;
- coordinate health care and clinical research efforts to increase the quality, completeness, and interoperability of eHR data;
- facilitate development of third-party data aggregation, health information exchanges,[28] or messaging services to exchange data among systems;
- clarify regulatory agency expectations;
- create a collaborative relationship between sponsors and investigative sites by developing eHR data use efforts incrementally and maintaining open communication with health care institutions; and
- enable a robust change management strategy, including educating parties regarding the benefits of eHR use in clinical research.

Conclusion

Based on survey results, companies have taken steps to leverage current eSource technologies and prepare for optimal utilization of electronic data sources. It is clear from the feedback from regulators, standards groups, and those TransCelerate members who participated in our eSource survey that there is a common goal to modernize the way we collect and work with data to develop supporting evidence for new drugs.[29]

The work of the TransCelerate eSource Initiative will focus on additional landscape development with regard to technological capabilities, regulatory requirements, standards, and health care considerations related to sites and patients. Positions or best practices will be established that focus on several areas that are critical to maximize use of eSource. Stakeholder engagement and change management practices inclusive of regulatory and health care agencies, sites, and patient groups are as important as discussions between technology companies and research sponsors. Considerations such as protection of subject rights, data protection, International Council for Harmonisation Good Clinical Practice requirements, interoperability, key performance indicators, and the results of demonstration projects are all important components of those discussions. All final work of the team will be made public either through the creation of specific articles intended for publication or through practical tools to assist with eSource implementation.

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Declaration of Conflicting Interests

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