ELLIGO® HEALTH RESEARCH | Goes Direct®

The System of Accelerated Research (SOAR™)

Expanding Patient Access and Driving Efficiency by Enabling Direct Data From Source to Submission

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Introduction

The process for developing and approving new therapies for patients has been under scrutiny for at least three decades; concern regarding a "broken" clinical research system has been voiced by many, including patients and caregivers. Despite global technological advances, the costs and efficiencies associated with bringing a new product to market are going in the wrong direction, (i.e., higher costs with longer cycle times). It is well-documented that research protocols are becoming more complex, the amount of data collected per study is increasing, and cycle times are getting longer (1). Many physicians conduct one study and no more due to excessive administrative burden. Prices for new drugs have skyrocketed.

What will it take to reverse this trend? The number of patients and physicians participating in clinical research must increase. New technology must be applied in novel ways to radically change the research process:

> *"Unfortunately, we've seen a continued reluctance to adopt innovative approaches among sponsors and clinical research organizations. In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive, but disruptive, changes that certain innovations can enable (2)." Scott Gottlieb, MD, former FDA Commissioner*

Standards for health care and clinical research need to be applied from the start and better harmonized, and other bridges must be built to more closely link research and health care.

To that end, the FDA and other regulatory agencies are encouraging the use of new technologies, electronic health records (EHRs) for research, eSource, real-world data, and decentralized trials (3). A recent FDA communication encourages innovation in lieu of the status quo.

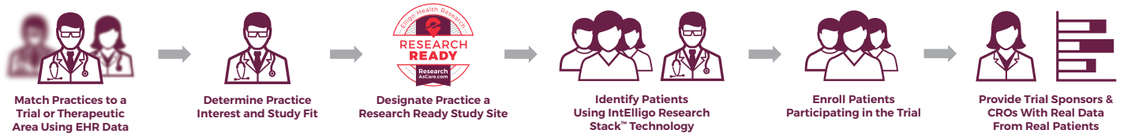
"The Machine That Changed the World" (4) makes the case for lean manufacturing vs. mass production and also for building quality in from the start. Recommendations from the re-engineering era (5) indicate that we must fundamentally change the existing paradigm by standing back and looking at the current process with a new lens, challenging our thinking in the context of newly available tools and opportunities.

This white paper first explores current issues with clinical research and the stimuli that are aligning to address them. It then describes the System of Accelerated Research (SOAR™), a transformative model that adheres to all required regulations while accelerating the overall research process, ensuring quality and integrity and focusing on the patient.

The Elligo ***Goes Direct***® approach (See Figure 1) and Elligo's approach to data sciences expands the capacity for research and removes administrative and data management barriers that have carried over from an antiquated paper-based approach. The IntElligo Research Stack™ technology platform accelerates study startup and protocol implementation, ensuring that data flows smoothly from source to submission. Streamlining protocol designs and focusing them around patients and care workflows take this approach one step further in terms of building in quality from the inception. Additionally, and most importantly, this approach enables Elligo to relieve physicians of administrative burdens and better serve patient needs — all while providing the infrastructure and capabilities for SOAR (See Figure 4).

Figure 1

The *GOES DIRECT*® Approach



Match Practices to a Trial or Therapeutic Area Using EHR Data

Determine Practice Interest and Study Fit

Designate Practice a Research Ready Study Site

Identify Patients Using IntElligo Research Stack™ Technology

Enroll Patients Participating in the Trial

Provide Trial Sponsors & CROs With Real Data From Real Patients

Key Current Issues

Issue 1: Participation of physicians and patients in clinical research studies is far too low.

Biopharmaceutical development is under constant pressure to find technologies, processes, and operating models that decrease cost, time, quality threats, and uncertainty in the drug development process. Regulated research continues to be burdened with an insufficient number of both physicians willing to be investigators and patients willing to participate in research. Studies are routinely delayed due to slow enrollment, which in turn negatively impacts the speed with which new therapies can be brought to patients and increases associated costs.

In 2010, Dr. Robert Giffin and Dr. Janet Woodcock authored a manuscript (6) in which they wrote: "…. by two important measures — the number of researchers conducting trials and the number of patients participating in them — our clinical trial capacity is declining."

Giffin and Woodcock cite several deterrents for the physicians doing research:

- Limited incentives
- Stiff challenges in execution
- Administrative burdens
- Level of effort not compensated by financial reimbursement

"…. by two important measures — the number of researchers conducting trials and the number of patients participating in them — our clinical trial capacity is declining."

Moreover, concerning their latter point, not only is reimbursement insufficient for the current level of administrative burden at a research site, but payments are woefully late from sponsors and clinical research organizations, which are asking a great deal of these research physicians; even insurance payments are speedier.

These challenges are particularly acute for those physicians unaffiliated with a dedicated research site or an academic research organization. Large hospitals, practices, community physicians, and others who could offer new therapies as a care option see significant barriers to engaging in clinical research. In their routine practices, there are myriad frustrations with threats to autonomy, poor or slow reimbursement for service, and excessive time required. Consequently, many physician investigators do one research study and no more. Furthermore, because they often have little time or interest to engage directly in research themselves, they do not make a recommendation for their patients to participate in research nor do they wish to make a referral to a research investigator.

Giffin and Woodcock also provide reasons why so few patients participate in clinical research:

- Few community physicians participate in research
- Patients have difficulty locating research studies on their own
- Patients prefer to be treated by their own physician and not referred to another physician
- Daunting informed consents
- Patient concerns that they may receive a placebo vs. the actual treatment

Few patients hear about research opportunities and, when they do, the protocols are not likely to move them from vague awareness to active participation. Our current patient outreach methods do not inform, engender trust, or engage patients adequately. Unwieldy expectations and lengthy informed consent documents are frightening deterrents.

While focus groups of patients and advocacy groups have raised consciousness about the issue, they have not increased patient participation. Reaching more patients will require going directly to the physicians, not just the patients.

Research offers potentially life-saving benefits or ground-breaking therapies to patients, but it seems to require a personal interest and a significant investment of personal time on the part of the patient or their health care provider to realize such benefits. Physicians must make the effort to seek out opportunities for patients and engage and implement these ideas and research studies with their patients, but doing so is a significant barrier and at odds with the current health care environment (7). Patients are even less likely to seek clinical research opportunities on their own unless they have a well-informed and/or knowledgeable support network.

Issue 2: Cumbersome clinical research processes may compromise integrity, data quality, and overall efficiency.

The clinical research industry has actually been referenced as a cottage industry due to the excessive redundancy involved (6). Specifically, many of the processes and procedures for each and every study are unnecessarily replicated.

Each data point collected in a research study may be entered and then re-entered three to seven times (8) and then manually verified. The regular employment of CROs and increasing use of technology applications (average of six per study) (1) have understandably resulted in built-in redundancies and duplication of efforts.

Protocols have become more complex and more data points are being collected per protocol than ever before. This has increased cycle times for database build, database lock, and other research processes (1). Despite the increasing use of new technologies, the current clinical trial process largely mimics prior paper-based processes with technology add-ons. In addition, source documentation at the investigative site continues

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to be primarily paper-based. The delay between the documentation of source data on paper and entry of that data into an electronic data capture (EDC) tool can create a potentially unsafe situation in addition to increasing the opportunity for error in transcription and delays in data access by sponsors.

Combined with inherently inefficient and redundant processes, an inadequate number of productive investigators and participating patients puts stress on the enterprise. Among the areas threatened are data quality and data integrity. When data are entered and then re-entered or transcribed multiple times, the chance of introducing errors increases, thus reducing data quality and introducing the need for additional edit checks, verification, and query resolution steps.

Further, when research sponsors feel the pressure of slow enrollment, increasing costs, and increasing uncertainty in completion dates, timeline-correcting maneuvers are employed that can also threaten data integrity. Protocols are amended, patients are enrolled with less than perfect protocol-fit, and attention that should be allocated to perfecting the site's implementation of the protocol may be diverted to recruitment activities. Quite rightly, regulatory authorities are increasingly demanding much greater data integrity control in addition to the ongoing requirement to maintain an audit trail from source data to regulatory submission.

Issue 3: Inadequate bridging of patient care with clinical research exacerbates an ineffective and costly health care ecosystem.

Contemporary clinical researchers put considerable thought and effort into designing protocols that follow treatment guidelines and best practices. In addition, the careful and detailed medical examinations required for complex inclusion decisions go beyond what most patients experience in routine practice. As such, participation in a clinical trial can offer not just new and otherwise unavailable (albeit, experimental) therapies, but comprehensive medical care as well. That said, in the pursuit of a pure sample for research purposes, overly stringent protocol inclusion/exclusion criteria may create an unattainable patient profile that results in numerous protocol deviations and violations, delays, and additional costs in order to enroll the trial.

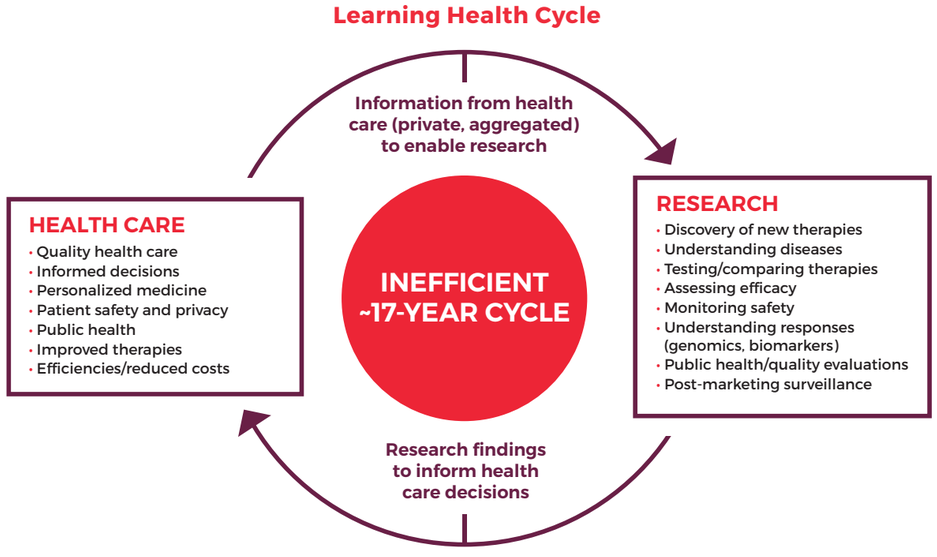
Enrolling patients into research studies that do not reflect routine patient care while incorporating numerous additional procedures may provide useful information about new procedures or therapies; however, this may also create unnecessary aberrations in the lives of patients so as to render the study impossible to enroll an adequate number of patients or physicians willing to participate. This is self-defeating and creates a research population that is not typically representative of the real-world population intended for the new product.

Identifying patients for clinical research through EHRs and health care data and using that data directly for regulated research holds promise, but thus far has been limited and not routine. Concerns remain about completeness, adequacy, format, and quality of EHR data and regulatory acceptance. The use of real-world data has been primarily focused on post-marketing and safety surveillance studies. In addition, EHR data are typically re-entered into source documents, clinical trial management systems, and EDC systems. A lack of harmonized standards/semantics between health care and research continues to be a barrier to direct use of EHR data for research.

The increased use of mobile devices also is somewhat encouraging. Such devices can collect digital data directly from patients, whether through ongoing measurements such as glucose monitors or through patient reported outcomes such as e-diaries. Unfortunately, however, a risk-adverse industry has a tendency to treat much of this data as an accompanying source of information as opposed to critical study data.

Bridging health care and clinical research has been a dream since EHRs emerged in the 1980s. Efficiencies that can be gained through "bridges" that enable the use of health care data for research to inform patient care have been documented (9,10,11). However, such bridging has been inadequate to date. Incentives are misaligned when EHR vendors maintain data in proprietary formats; when vendors increase revenues through customization of EHRs by practice/customer or by treating patient data as an asset rather than acting as a trusted guardian; or when users focus on the requirements for billing rather than patient care in their feature sets. Inadequate bridging without putting the patient first continues to exacerbate the inefficient and costly health care culture we experience today.

Figure 2



Stimuli Aligning to Enable a Transformative Research Model

A typical learning health cycle includes the collection of health care data to support a research hypothesis/protocol, aggregation and analysis of these data, and communication of the results/learnings such that the most current and robust information can be considered by health care providers and patients to optimize care and improve health (See Figure 2). This is a very inefficient cycle, purported to take 17 years. Clearly, more rapid learning health cycles (or knowledge turns) will benefit all of us.

Despite the aforementioned issues, stimuli from both within and outside of the research space are beginning to align and enable a transformative model such as SOAR. Three such stimuli are described as follows.

Stimulus 1: Bridging health care and research to accelerate learning health cycles will benefit patients.

In her keynote presentation at the Bridging Clinical Research & Clinical Health Care Collaborative in April 2018 (11), Dr. Janet Woodcock, director of FDA/CDER, proposed five "bridge features" for bridging research with health care:

1. The patient and treating physician should be at the center.
2. Research should be integrated into the workflow of patient care.
3. Data must be robust by intent, not by quality control (QC).
4. Consent and randomization should be integrated into a digital environment.
5. There should be "rapid knowledge turns."

More rapid knowledge turns are the underlying intent of learning health systems, which have been defined by the Institute of Medicine as systems in which "science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience" (13). Since this definition was developed, the Learning Health Community (LHC) has published consensus-based Core Values of a Learning Health System (14).

Overarching goals for bridging research and health care to accelerate learning health cycles are to develop and understand new therapies more rapidly while slowing the upwardly spiraling costs associated with regulated research and health care. This will require leaders to go beyond the existing structure to try new methods

that leverage technology in new ways, and will require aligning incentives. Patients will benefit when the cost of health care decreases and they have more rapid access to safe and effective therapies, along with more robust and meaningful information upon which to base their health care decisions.

Stimulus 2: Technological advances of the recent decade are enabling processes and opportunities not previously available for research.

The dramatic increase in computing power and communications, along with the increased adoption of EHRs, makes accessing data on millions of people more affordable and feasible. Big data analytics, artificial intelligence, natural language processing, and machine learning increase the potential to interrogate these data using increasingly sophisticated algorithms that can inform the design of more appropriate protocols, match rich patient data to protocols to identify qualified patients, and monitor study data for safety signals and quality.

Such advances in technology now allow us to envision systems that will improve and accelerate research. It is important, however, to integrate the technology into processes in a manner that does not simply follow the current processes; rather, the implementation must be new and innovative. We must step back and look through a new lens at process redesign when applying new technologies to a process that has thus far largely mimicked the original paper-based process. The new technology-enabled processes must radically change the current paradigm while leveraging ongoing technological advances and adhering to appropriate regulations.

Another consideration is to ensure that the new system adopts an iterative approach, including a glide path for future standards and technology and continuous improvement. The *kaizen* principle from Japan, through which a business can continuously improve by engaging input from all stakeholders at all levels of the process, comes to mind. *Kaizen* has been applied to continuously improve clinical pathways (patient care protocols), which is the first step toward accelerating learning health cycles (15).

Stimulus 3: Harmonized, global clinical research data standards are available.

Over the past two decades, the development of global standards for clinical research has made significant progress, and the advantages of using standards have been documented (16,17). The U.S. FDA and Japan's PMDA now require CDISC data formats for regulatory submissions. The use of data standards from the start (i.e., from the protocol development and CRF design stages) has been shown to significantly reduce study startup time and streamline data flow throughout the entire process, from protocol through submission.

Unfortunately, no global data standard exists for health care; many EHRs use proprietary data models. HL7 introduced Fast Healthcare Interoperability Resources (FHIR) to enable standardized exchange of data among EHRs using an API approach (18). While there is much enthusiasm around FHIR, there is still work to be done in the development of FHIR resources and semantics that will support the use case of regulated research. Recent rules have been proposed through the U.S. Department of Health and Human Services to require that patients have access to their electronic health information, and FHIR has been recommended for this purpose. It is hoped that this may stimulate more standardization within the U.S. health care arena. In the meantime, Japan has a standard for storing health care data called SS-MIX, which has been leveraged to produce CDASH (the CDISC data collection standard) for research studies (19).

A collaboration of NCI, FDA, HL7, CDISC, and ISO produced a robust data model called the Biomedical Research Integrated Domain Group (BRIDG) model (20). This model is now a global standard within ISO, HL7, and CDISC. It is being used as the central model in an FDA-led project, funded through the Patient Centered Outcomes Research (PCOR) Trust Fund, to harmonize common data models (specifically models from OHDSI/OMOP, Sentinel, i2b2, and PCORNet) (21). The goal is to make it easier for data to be provided for research from existing EHRs and data repositories and ultimately to be received by FDA in the required format.

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In addition to data standards, the Alliance for Clinical Research Excellence and Safety (ACRES) has recently posted a site quality standard through the British Standards Institute to encourage quality among research sites/investigators. This standard takes a quality systems approach that can potentially help alleviate the need for redundant evaluation visits to sites that have demonstrated such quality.

The System of Accelerated Research (SOAR™) – Modules and Characteristics

While not fully mature, the aforementioned stimuli are aligning, along with the interests of regulators, research sponsors, physicians, patients, caregivers, and advocacy groups, to provide energy and resources to transform the current research process. The System of Accelerated Research (SOAR) illustrates such a process (See Figure 3).

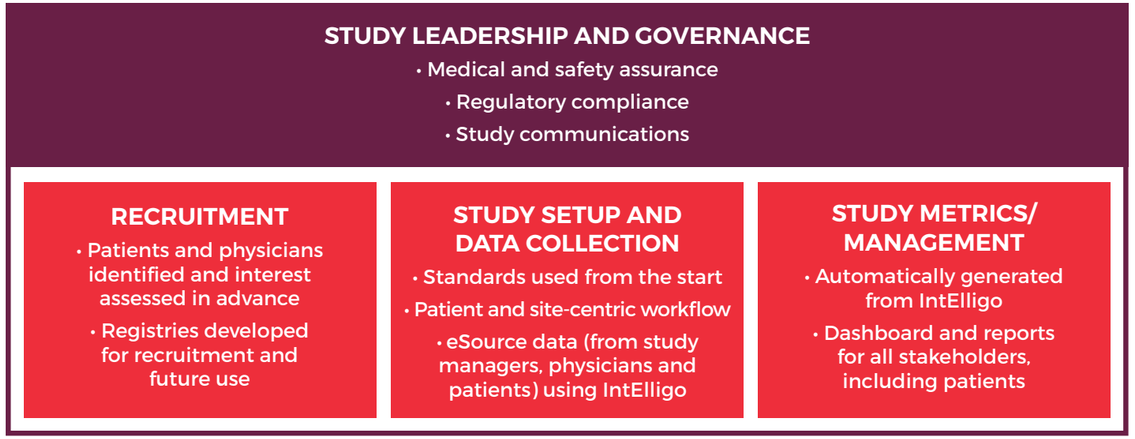
As a transformative model that accelerates the research process, SOAR:

- Solves problems that vex the industry
- Bridges research and health care
- Leverages real-world data and new technologies
- Is innovative and fits well in the rapidly evolving ecosystem of virtual models and decentralized trials
- Adheres to existing regulations and upholds scientific integrity

SOAR is comprised of four core modules that focus on:

- Leveraging real-world evidence to accelerate patient/physician engagement
- Standardizing and streamlining the flow of data from source to submission
- Automating real-time study and management information
- Enabling medical oversight, governance, and communication avenues for sponsors, patients, and physicians

Figure 3



Characteristics inherent in SOAR:

- **SOAR is transformative:** Recruitment will be completed in a fraction of the time compared to a similar trial using the legacy model of clinical research. In one case study, lagging enrollment was rectified when Elligo used real-world data to identify qualified patients within three days of IRB approval and prior to the targeted date for enrolling the first patient.

Referred qualified patients 3 days after IRB approval and 5 days prior to Sponsor Target Date for Study Start

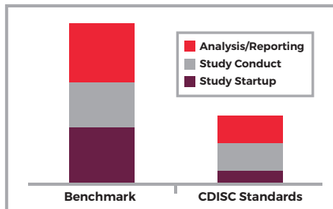
- **SOAR is patient-centric and respectful of the physician-patient relationship by design:** The patient stays with his/her trusted physician throughout the study, with the aid of trained study managers to offload the administrative burden. Below are results from a survey of physicians who had not previously conducted research:

88% of physicians were interested in piloting SOAR™

82% of physicians said they would allow Elligo to contact their patients on their behalf to discuss joining a study

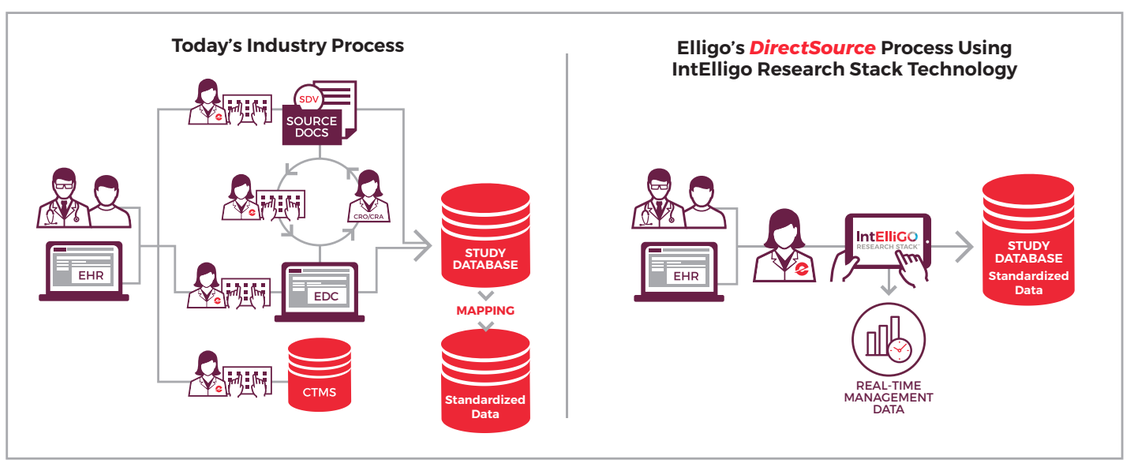
88% of physicians were willing to enter data into a portal for a clinical trial

- **SOAR is powered by a robust technology platform:** The IntElligo Research Stack™ platform is built to meet strategic goals, including rapid study setup, centralized data integrity control, streamlined standard data flow from eSource to submission-ready data, treatment of patients in their homes or where they normally go for their health care, and processes customized to align with physician workflows.



Study Startup is
70-90% Faster
Using Standards From the Start

- **SOAR significantly reduces data transcription and time to access study data and management information.** Data is entered once as standardized eSource data by the Elligo study manager, patient, or physician (as appropriate), compared to today's process through which data is entered and/or transcribed 3-5 times. Thus, SOAR improves data quality and provides real-time information to improve medical monitoring and study management.



- **SOAR is fit for complex medical situations and indications requiring meaningful medical oversight:** The focus is on real-world patients in community practices, while protecting the internal validity of the trial through robust procedures and readily available source data to facilitate prompt medical monitoring.

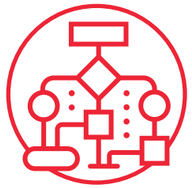
- **SOAR is fit for regulated trials, registration trials, and post-marketing trials:** SOAR is designed with all of the principles of ICH E6(R2), 21CFR11 and other relevant regulations, undergirding the process and technologies controlling the flow of data.

- **SOAR enables learning health systems:** Learnings from the research are summarized and provided to patients and physicians at appropriate times during and after the study.

SOAR leverages the *Goes Direct* approach to match Elligo practices to trials; to match patients to trials through Elligo's data sciences services using real-world data; and to enroll real-world patients at real-world practices resourced with trained Elligo study managers.

The patient and physician are at the center

Quality and standards-based data are integrated from the start



Workflow is centered on the patient and health care provider

Informed consent is integrated and the process simplified

Learning health cycles are more rapid

Elligo Health Research and SOAR

Elligo Health Research, an integrated research organization, developed its ***Goes Direct*** approach based upon concepts recommended by Dr. Woodcock (12). Specifically:

- The patient and physician are at the center
- Quality and standards-based data are integrated from the start
- Workflow is centered on the patient and health care provider
- Informed consent is integrated and the process is simplified
- Learning health cycles are more rapid

Elligo can enable sponsors to gain the benefits of the innovations made possible with SOAR while forming bridges between research and health care. Through its ***Goes Direct*** approach, Elligo expands the capacity for research and removes the administrative barriers that have carried over from an antiquated paper-based process.

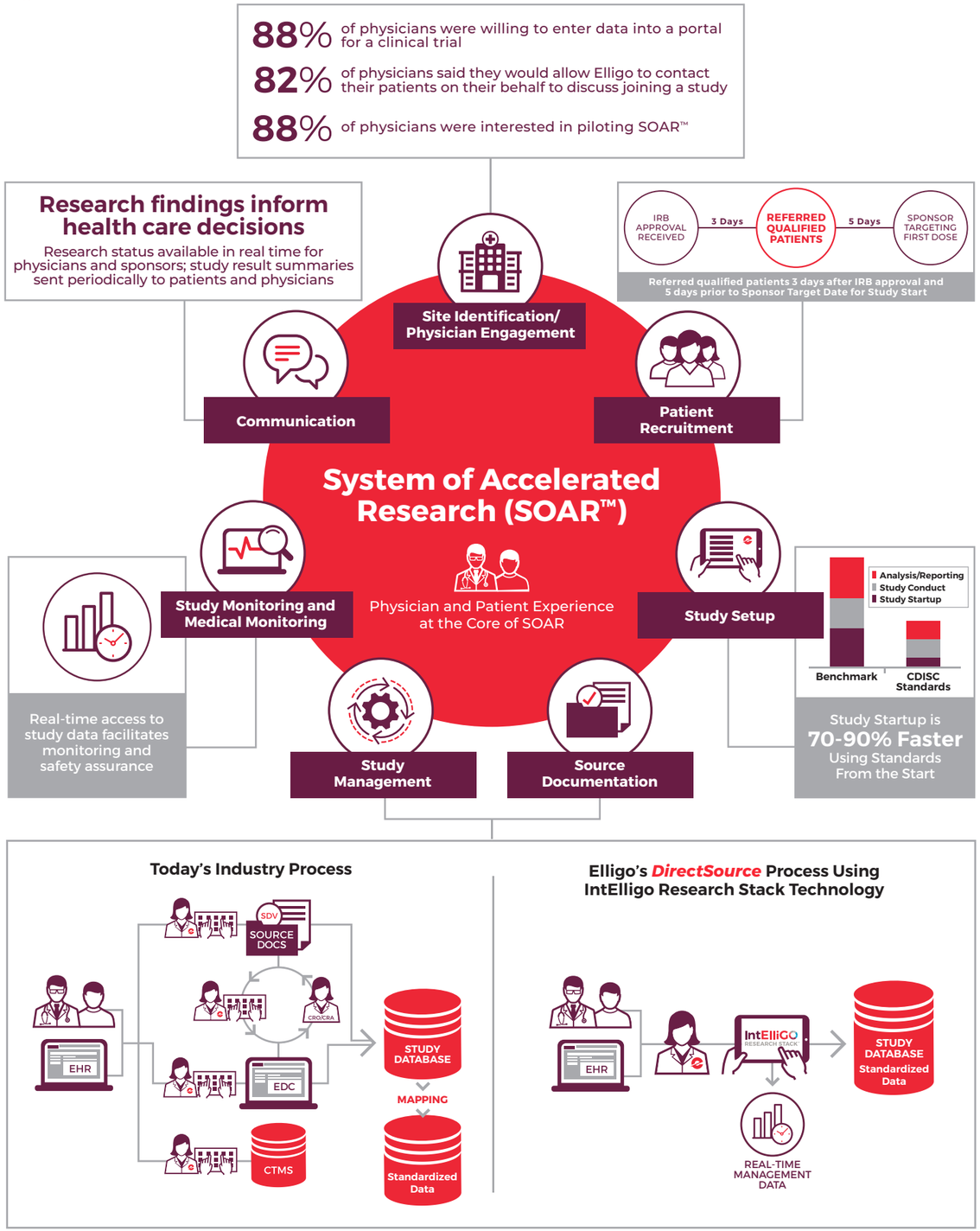
This innovative methodology arose from a comprehensive analysis of the current research system and infrastructure. A thoughtful redesign approach was applied to resolve the aforementioned issues with key goals to accelerate the research process, adhere to all relevant regulations, and improve data quality and data integrity while focusing on the patient and physician dyad.

The IntElligo Research Stack technology platform accelerates study startup and protocol implementation, ensuring standard data flow from eSource to submission-ready data. Quality is built in from the start and, most importantly, the process is tailored to relieve physicians of the administrative burdens of doing research and allow them to better serve patients' needs.

SOAR leverages the IntElligo Research Stack technology platform and data sciences services, which have been developed and are currently led by experts who have spent decades in the industry. These experts have worked with thousands of patients and physicians; they have experience in process analysis, redesign, and re-engineering; they have been research sponsors, partners, academic research organizations, technology providers, service providers, and standards developers. This deep and varied experience has enabled Elligo to view the issues anew and comprehensively, align the appropriate stimuli, and develop SOAR.

Truly innovative and transformative, SOAR provides research sponsors the opportunity to approach research in a comprehensive way and replace a system that has been broken for far too long. We owe it to the patients who participate in research to treat their time and their data responsibly.

Figure 4



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About Elligo

Elligo Health Research, an integrated research organization, expands access to clinical research by bringing together health care data, community physicians and their patients. Only Elligo's ***Goes Direct***® approach and IntElligo Research Stack™ clinical technology — a complete standards-based technology solution — deliver better patients and improved real-time data through Elligo's network of Research Ready sites within its Communities of Research. Learn more at elligodirect.com.