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A conceptual model for the development process of confirmatory adaptive clinical trials within an emergency research network

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Abstract

Background—Adaptive clinical trials use accumulating data from enrolled subjects to alter trial conduct in pre-specified ways based on quantitative decision rules. In this research, we sought to characterize the perspectives of key stakeholders during the development process of confirmatory phase adaptive clinical trials within an emergency clinical trials network, and to build a model to guide future development of adaptive clinical trials.

Methods—We used an ethnographic, qualitative approach to evaluate key stakeholders' views about the adaptive clinical trial development process. Stakeholders participated in a series of multidisciplinary meetings during the development of five adaptive clinical trials, and completed a Strengths-Weaknesses-Opportunities-Threats questionnaire. In the analysis, we elucidated overarching themes across the stakeholders' responses to develop a conceptual model.

Results—Four major overarching themes emerged during the analysis of stakeholders' responses to questioning: the perceived statistical complexity of adaptive clinical trials, and the roles of

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Declaration of conflicting interests

Dr. Berry reported that he is part owner of Berry Consultants LLC, a statistical consulting firm that specializes in the design, implementation, and analysis of Bayesian adaptive clinical trials for pharmaceutical manufacturers, medical device companies, and academic institutions. Dr. Lewis reported that he is the senior medical scientist for Berry Consultants LLC; both Dr. Lewis and the Los Angeles Biomedical Research Institute are compensated for his time.

Author contributions

SM drafted the manuscript. MJF and LL supervised and designed the data collection. WJM, TG, MJF, SM, SMF, and LL analyzed and interpreted the data. SMF and SM were responsible for project administration. WB, RKJ, and DB obtained funding and supervised ADAPT-IT. All authors read and approved the final manuscript providing feedback on key intellectual components.

collaboration, communication, and time during the development process. Frequent and open communication and collaboration were viewed by stakeholders as critical during the development process, as were the careful management of time and logistical issues related to the complexity of planning adaptive clinical trials.

Conclusions—The Adaptive Design Development Model illustrates how statistical complexity, time, communication and collaboration are moderating factors in the adaptive design development process. The intensity and iterative nature of this process underscores the need for funding mechanisms for the development of novel trial proposals in academic settings

Keywords

Adaptive clinical trials; confirmatory-phase clinical trials; mixed methods; SWOT; qualitative research; neurology clinical trials

Introduction

Concern for high failure rates in the drug development arena prompted the U.S. Food and Drug Administration (FDA) to release a *Critical Path Opportunities List* in March 2006, which discussed key areas to improve in the evaluation of FDA-regulated medical products.[1] The *List* identifies Adaptive Clinical Trials (ACTs) as an innovative way to potentially improve the success rate of drug discovery and development. ACTs differ from conventional randomized control trials which use fixed design parameters, e.g., randomization procedures, dose, and treatment arms that are defined at the beginning of the study and held constant during the trial. In ACTs, key parameters can be altered as data accumulate, according to pre-planned decision rules. As knowledge improves, modifications are made which can increase the likelihood of a more efficient, accurate and successful clinical trial.[2] The ethical and statistical advantages and disadvantages of ACTs continue to be debated. Advocates of the methodology argue that ACTs can improve the ethical balance between risk and benefit for individual patients, since fewer subjects may be exposed to potentially risky therapies, and more patients are assigned to better-performing treatments as more data are collected. Critics counter that ACTs potentially increase patient exposure to research procedures and drugs that may remain unproven at the end of the trial. Further, they express concern that ACTs invite therapeutic overestimation, and introduce various validity threats.[3–5]

In an effort to encourage broader acceptance of ACTs, the National Institutes of Health (NIH) and FDA funded the Adaptive Designs Advancing Promising Treatments into Trials (ADAPT-IT) project in September 2010.[6] The primary aim of ADAPT-IT was to explore how to use adaptive clinical trial designs to improve the development of drugs and medical devices, specifically in the care of patients with acute neurological illness or injury. Included in the planning grant were five confirmatory-stage clinical trials: ARCTIC –Acute Rapid Cooling for Traumatic Injuries of the Cord; DCCSCA – Duration of Cooling in Comatose Survivors of Cardiac Arrest (now ICECAP – Influence of Cooling duration on Efficacy in Cardiac Arrest Patients; ProSPECT – Progesterone in Acute Stroke; SHINE – Stroke Hyperglycemia Insulin Network Effort; and US-SETT – United States Status Epilepticus Treatment Trial (now ESETT – Established Status Epilepticus Treatment Trial). These trials

were proposed for implementation through the NIH-funded Neurological Emergencies Treatment Trials (NETT) network.[7, 8]

The secondary aim of ADAPT-IT was to utilize a mixed methods approach to characterize and understand the beliefs and opinions of stakeholders about the development process of ACTs. Despite the potential of ACTs, surprisingly little research had been conducted about the process of planning, implementing and running them. Two groups identified barriers to implementing adaptive designs in the commercial pharmaceutical research and development industry.[9, 10] They identified five barriers to implementation: 1) requirement of additional planning time; 2) willingness of the project team to engage in additional activities involved in conducting clinical trial simulations; 3) availability of statistical and clinical expertise, and software tools; 4) impact of adaptive approaches to functional lines supporting clinical development, e.g., drug supply, management; 5) insufficient top-down motivational and financial support from the research and development organization to build a scalable infrastructure enabling adaptive approaches.

Few authors have examined the use of adaptive designs in clinical trials that are developed in the academic setting. To narrow this gap, the ADAPT-IT mixed methods team identified key stakeholders' perceptions about ethical benefits and potential ethical disadvantages of adaptive designs in confirmatory phase trials within an academic, emergency research network.[3] In further work, the team illustrated how the ACT development process itself educates stakeholders who are unfamiliar with adaptive designs, and the need to utilize feedback mechanisms among collaborators, and to iteratively change the planning process as needed.[11] In a study from the United Kingdom, Dimairo et al. explored key stakeholders' perceptions about adaptive designs in confirmatory phase trials within the publicly funded setting.[12] They found that researchers perceived benefits of adaptive designs in various therapeutic areas, but that a lack of experience, practical knowledge, applied training, operational and statistical complexities and minimal access to case studies were barriers to planning and implementing adaptive designs.

The purpose of the current research was to expand on these previous findings about ACT development from both the private and public clinical research sectors. From the identified major themes, we developed a conceptual model of key factors influencing the effective development of ACTs, thereby assisting researchers who are planning novel adaptive designs.

Methods

Design

Understanding the adaptive design development process from the key stakeholders' perspective was an integral component of the ADAPT-IT project. This study was part of an overarching mixed methods evaluation of the development process.[7] Grounded in ethnography, we used a qualitative Strength-Weaknesses-Opportunities-Threats (SWOT) data collection framework and field observations to collect data during the development process of five adaptive design trials in the ADAPT-IT project. The SWOT framework has been widely used in business, education, community needs and resource analyses, and in

social science research. The SWOT framework can be used to identify factors that are perceived to exert an impact on a specified objective.[13] Due to their relative simplicity and applicability to a variety of areas, SWOT analyses can be used to identify problems, reveal priorities, and explore positive aspects in various settings.[13] The ADAPT-IT project was determined to be exempt from oversight by the University of Michigan Institutional Review Board under Federal regulations allowing survey research. Respondents to all instruments consented verbally prior to the initiation of data collection. Prior to meetings, we provided participants in ADAPT-IT with information about the mixed methods team observation during meetings and the use of those field observations for research.

Participants

Key stakeholders were drawn from a group of clinical trial experts. Each proposed trial was comprised of Principal Investigator and Co-Investigator- led clinical teams from multiple institutions. Other key stakeholders included academic biostatisticians and clinical leaders with extensive experience in conducting confirmatory phase trials, from within the Neurological Emergencies Treatment Trial network. Their role was to provide leadership and oversight throughout the proposed trials' implementation within the NETT network of clinical sites. Adaptive design consultant statisticians from industry, with extensive experience in developing adaptive designs provided the statistical expertise in modeling for each proposed trial, after input from the NETT leadership, NETT clinical leaders and biostatisticians, and the clinical team for each proposed trial. Finally, partners from the NIH and FDA, and patient advocates, guided the key stakeholders during the design process with their unique perspectives about funding, regulatory review of ACTs, and patient-related issues. Generally, the NETT leadership, academic biostatisticians, consultant statisticians, and regulatory partners were the same across the proposed trials, while each study's clinical team was comprised of different clinicians who were experts in the disease of interest (Table 1).

Setting

The ADAPT-IT development process consisted of four phases for each trial: an initial face-to-face meeting, concept teleconferences, a performance workgroup held virtually, and a second face-to-face meeting.[7] Face-to-face meetings in various cities occurred between January 2011 and February 2013. At the initial face-to-face meeting, study clinical teams presented slides about the studies focusing on the clinical need and existing clinical and pre-clinical scientific basis to initiate the discussions. The adaptive design consultant team provided a general introduction to adaptive designs. Then, the group discussed preliminary ideas for incorporating adaptive design strategies into the trials. Next, a series of concept teleconferences were held concurrently over the two years for each of the five trials, between January 2011 and February 2013. Key discussions during the concept teleconferences included: an initial adaptive design conceptual overview for the specific clinical trial proposal; goals for each trial and proposed adaptive features (for example dose response modeling and predictive longitudinal modeling of the outcome); strengths and weaknesses of the proposed adaptive design; areas for further development, incorporating guidance from the clinical team; presentation of simulations; and the identification of key process outcomes. During the performance workgroups for each trial, consultant statisticians

reviewed trial simulations and provided feedback. Finally, additional face-to-face meetings occurred, during which each team presented and discussed the final versions of the adaptive trial design. The participants at the second face-to-face meeting varied for each trial, depending on the availability of the stakeholders. At least one Principal Investigator or Co-Investigator from each clinical team attended all of the face-to-face meetings. After comparing the original protocol design, with the advantages, disadvantages, and logistical requirements of each design which was created during the ADAPT-IT process, clinical teams decided whether to incorporate the proposal or its elements into their clinical trial protocol. The designs could either be entirely implemented in the clinical trial, or could simply be used to inform important improvements in the final protocols. Specific types of adaptations used within the ADAPT-IT trials included – longitudinal modeling of outcomes, response adaptive randomization (used to allocate more patients to better performing treatments in a three-arm comparative effectiveness trial), dose-response modeling (used to estimate the shortest duration of hypothermia that provided the most neuroprotection), enrichment (used to restrict enrollment to those patients who were likely to benefit from the treatment), and hierarchical modeling (used to conduct a phase II trial of glycemic control in different stroke subtypes while borrowing information from an ongoing phase III ischemic stroke trial). All included quantitative decision rules for early stopping for futility, and in some cases efficacy.

Observers on the ADAPT-IT mixed methods team documented the concepts that were discussed during conference calls and observed the group processes and interactions during each meeting.

Data collection

Following each face-to-face meeting, key stakeholders responded to a self-administered, free-text SWOT survey via an online survey program (Qualtrics™). The following questions were asked of participants:

1. What were the strengths the adaptive trial design process used within ADAPT-IT?
2. What were the weaknesses of the adaptive trial design process used within ADAPT-IT?
3. What were the opportunities of the adaptive trial design process used within ADAPT-IT?
4. What were the threats to the adaptive trial design process used within ADAPT-IT?

Data analysis

We identified emerging themes from the data and created a summary table from the stakeholders' responses using a qualitative analytic approach of immersion/crystallization.[14, 15] The analysis was not organized by question, since themes in a single response frequently had broader implications and addressed topics beyond the focus of the question itself. Responses were divided into three main categories: general commentary

about ACT designs; commentary about the ADAPT-IT process; and trial-specific commentary that addressed issues relevant to one of the five trials. The comments and field observations were then distilled into overarching themes and a narrative was developed to represent the stakeholders' views about the adaptive trials development process. The team sought to characterize and understand the perspectives, beliefs, opinions, and concerns of key stakeholders as they were developing ACTs, and elucidate a model of key factors influencing the development process.

Results

Four major overarching themes relevant to ACT trial development emerged based on the information provided by the stakeholders and team observations. The major themes related to the statistical complexity of ACTs, and the roles of collaboration, communication, and time during the ADAPT-IT projects.

The impact of statistical complexity and use of simulations on the ACT development process

Statistical complexity of adaptive designs emerged as a major theme (Supplementary Table 1). Some ADAPT-IT stakeholders did not have broad experience with the statistical modeling utilized by the consultant statisticians. To mitigate the impact of statistical complexity inherent in the methodology, statistical modeling or simulations were used as an important planning tool to clarify and improve understanding of complex adaptive design characteristics. In their responses, some clinicians and academic biostatisticians stated that they would have liked more opportunities to interact with simulations. Others preferred information about the simulations to be provided well ahead of time so that they could better prepare for meetings with the consultant statisticians. By using simulations during the development process, stakeholders could explore and compare performance characteristics among several competing designs, and therefore, be ready with specific questions regarding the adaptive design during face-to-face meetings. One study team clinician expressed an opinion that the face-to-face meetings would have been improved by more interactive presentations of the different designs by the consultant statisticians. A stakeholder from the regulatory group and a clinician would have liked more comparisons between and more information about Bayesian and non-Bayesian adaptive designs.

An issue deriving from the complexity is how to best communicate design features among the stakeholders. Statisticians, for example, identified two steep learning curves, both for themselves about how best to communicate the complex features of the adaptive design simulations, and for non-statisticians to understand adaptive design simulations. Similarly, clinicians wanted more consistent formats for presenting the simulation results and more interactive tools that could be used to alter inputs. The paucity of a standardized terminology and the lack of standardized operating characteristics and software presentation formats were seen as weaknesses of, or threats to the development process by several clinicians in the ADAPT-IT development process. Clinicians stated that more context and real-world experiences that showed how traditional trials were improved by adopting adaptive designs were needed in order to foster more buy-in. These findings are important because a lack of

mutual understanding of the complex adaptive design concepts leads to resistance to the methodology, and can hinder the broader acceptance of ACTs.

The role of collaboration in the ACT development process

Collaboration also emerged as a major theme (Supplementary Table 2). In the first faceto-face and concept teleconference meetings for the trials, the discussions between consultant statisticians and academic biostatisticians were heavily focused on statistical parameters as both groups of statisticians were meeting for the first time. In subsequent meetings, the consultant statisticians and academic biostatisticians met separately first and this gave more time for collaborative discussions involving the clinicians in face-to-face meetings. The clinical teams identified the need to clearly communicate the problem under study to the statisticians and to develop a design that answered the right questions. Increased collaboration via email or teleconferences helped to increase the sophistication of discussions at the face–to-face meetings.

According to the stakeholders, diverse, interdisciplinary expertise among the clinicians, statisticians, and regulatory partners within ADAPT-IT increased the potential to develop better, more efficient ACTs that were more likely to succeed. Broad and collaborative input and support from diverse stakeholders were seen as major strengths of the process because they allowed the study team to anticipate potential concerns and future barriers, and become aware of alternative approaches. A critical area that was identified by key stakeholders was regarding early collaboration with, and support from, regulatory groups. From a regulatory perspective, interacting with the FDA during study planning was deemed as particularly important for more complex adaptive design studies.

The role of communication in the ACT development process

The importance of communication in the development process of ACTs was emphasized by various stakeholders (Supplementary Table 3). From one academic biostatistician's standpoint, a specific strength of the adaptive design development process was the greater level of communication between statisticians and clinicians. Effective communication was essential in order to frame the project goals, and was a starting point from which critical areas of uncertainty (such as the trial's sample size, best duration of treatment, and outcomes) could be determined. Fostering communication resulted in thorough discussions with knowledgeable participants that enabled the teams to identify multiple challenges facing each trial, and consider strategies to address these challenges within the designs. An example of a process that helped foster open communication among the teams was ensuring that as many different stakeholders (e.g. NIH and FDA partners, clinician leaders, consultant statisticians, and academic biostatisticians) as possible were present during concept teleconferences and face-to-face meetings. An opportunity identified by both clinicians and biostatisticians was for even more frequent exchanges of information, in order to ensure that all the stakeholders heard different viewpoints from each other. Several key stakeholders expressed that the ADAPT-IT development did present opportunities to discuss alternative approaches during the design development process. However, one stakeholder cautioned against meetings where there were "too many cooks in the kitchen", suggesting that though

communication is an important factor, too many varied or dissenting viewpoints could adversely impact progress.

Key stakeholders felt that communication between Bayesian and non-Bayesian statisticians needed to be more open. The lack of clear communication, particularly around decisions of which outcome measures to use and how to represent the outcome measures mathematically, was identified as a weakness and a threat to the development process.

The role of time in the ACT development process

Time limitations during the development process emerged as a fourth theme in the analysis (Supplementary Table 4). Allowing adequate time for clinical discussion and sharing of methodology early with all parties was seen as an essential part of the process. As discussed above, statistical modeling by using simulations can be a crucial tool to understand the potential performance of complex adaptive designs. However, the process of simulating over a range of potential scenarios regarding treatment effect, accrual and other key parameters, is time-intensive and requires bidirectional feedback between clinicians and statisticians. Stakeholders felt that there was not enough time during presentations of simulations to fully discuss the possible scenarios in various adaptive design models. As a result, they could not readily work out the details of the models which were being presented, or carefully consider all the possibilities. Having sufficient time to address questions and concerns about the designs during the development process was critical. The stakeholders' responses highlighted the necessity to plan for sufficient time in which to discuss not only the methodology, but also the logistical implications of choosing certain adaptive designs.

Development of the Adaptive Design Development Model

The Adaptive Design Development Model incorporates these four major themes as key factors in an effective ACT development process (Figure 1). As illustrated by the figure, the four factors are interrelated. The statistical complexity of adaptive designs requires continuous collaboration and communication during the iterative development process and these factors require sufficient time. Importantly, our analysis of key stakeholders' perspectives suggests that as the adaptive design becomes more complex, collaboration, communication, and additional time for simulations are even more valuable.

Discussion

The unique aspect of the ADAPT-IT project, and this analysis, is that we delved into the experiences and perspectives of academic researchers while they were actively engaged in the development process of confirmatory phase neurological emergencies clinical trials. Our research expands upon previous work by highlighting the impact of statistical complexity and the role of collaboration and communication. In our experience, collaboration was best achieved through face-to-face meetings during the iterative development process. To mitigate the impact of statistical complexity inherent in the methodology, statistical modeling or simulations were used during these meetings. Simulations are an important planning tool to clarify and improve understanding of complex adaptive design characteristics.[16, 17] Incorporating adaptive designs into trials requires that stakeholders

from multiple disciplines invest adequate time it to effectively communicate and understand complex design parameters. Input from multiple key stakeholders, including clinicians, statisticians, patient advocates, and regulatory partners was an integral part of the development process. From a regulatory perspective, interacting with FDA during planning is particularly important for more complex adaptive designs.[18] We elucidated a model which illustrates the role of statistical complexity, time, communication and collaboration during the development process. An implication of the model is that the more complex the adaptive design, the greater the need for iterative collaboration, communication, and statistical modeling, all of which require more time.

Before this research, the factors influencing successful development of confirmatory adaptive trials were not fully known or understood. Based on this research, we now have a conceptual modeling linking the major factors influencing ACT development. The importance of these elements, to a degree, has been reported in previous research. For example, in the pharmaceutical industry setting, Quinlan identified barriers to the acceptance of ACTs including: a lack of experience with ACT methodology; time limitations; and various technical and operational concerns associated with adaptive designs, the latter being factors necessary for implementation. Quinlan et al. recommended formally incorporating a simulation strategy as part of the planning process, and approximately 3 months of additional upfront planning time into project management timelines.[9] Our research during ADAPT-IT suggests that an upfront development process timeline of at least 3 months, and possibly longer, may be more realistic in the academic setting (Table 1). Dimairo et al. highlighted individual and organization obstacles in the successful implementation of ACTs, and identified cross-disciplinary conservatism as one of the major barriers to the uptake of ACTs in the confirmatory phase in the UK publicly funded environment.[12] Their conclusions reinforce statistical complexity as a perceived barrier, and illustrate how collaboration and communication are needed for success during the development process.

Adaptive designs are complex, and require more advance planning and more time between initiating planning and starting the study.[19] Building the infrastructure and statistical expertise that is required to develop adaptive designs, select the appropriate models, and perform simulation studies during the design phase represents another challenge to the broad implementation of ACTs, particularly in academic settings where funding is limited. Additional time is necessary to fully tackle technical and logistical issues such as: programming language to handle adaptive designs within study databases and other data management issues; training of sites; strategies to maintain blinding; drug supply estimation; management of study drug inventory, and other pharmacy issues.[20, 21] The additional time and upfront development costs raise questions as to the feasibility of designing adaptive design trials without external funding to support the required infrastructure and expertise, even within the framework of a well-funded project such as ADAPT-IT. While planning and development in the pharmaceutical industry has direct funding from within the pharmaceutical company, specific funding streams for the development phase of an adaptive clinical trial are more difficult to establish in academic settings.

Ultimately, adaptive trials represent an innovative shift in the design of confirmatory phase research that has the potential to achieve greater financial efficiency in the long term.

However, the up-front costs of this research must be covered in order to achieve long-term savings. The intensity and iterative nature of the adaptive trial development process suggests that an innovative shift in funding mechanisms to support such trials is overdue. [22–24]

Limitations

The ADAPT-IT project was conducted within the context of a single, academic network with a focus on confirmatory phase, neurological emergency treatment trials in the United States. The Neurological Emergencies Treatment Trials network may not be a typical environment for the design of an adaptive clinical trial in an academic clinical trial center, given its existing infrastructure and access to key stakeholders who have experience in designing ACTs. Although it is likely that there will be similarities, our findings may not be generalizable to research networks specializing in different disease states, earlier phase trials, or clinical research networks in other countries. Also, direct comparisons of the development process between academia and industry may not be possible due to different funding models and mechanisms. However, other issues such as mitigating the issues of complexity during the development process are likely applicable to multiple settings. Further research will deepen our understanding of the adaptive design development process in multiple settings.

Conclusion

The primary aim of this article was to explore stakeholders' perspectives on the process of developing adaptive designs during the ADAPT-IT project. Two of the trials developed during the ADAPT-IT project, US-SETT (now ESETT) and SHINE, received funding and are currently enrolling subjects.[25, 26] SHINE included additional interim analyses based on the ADAPT-IT process. Although the Bayesian adaptive design was not implemented, it will run virtually as prospectively defined prior to initiation of the trial.[16]

The progesterone in acute traumatic brain injury trial within the Neurological Emergencies Treatment Trial network was stopped for futility and that outcome altered the enthusiasm for other planned trials examining the effect of progesterone in the brain.[27] As a result, investigators did not pursue grant submission for ProSPECT following the ADAPT-IT project.

The ARCTIC trial received an equivocal review, and investigators are considering whether to pursue another submission. DCCSCA (now ICECAP) investigators are preparing for grant submission; the protocol was submitted to the FDA and investigators may proceed under an investigational device exemption which was granted for the study. Future papers are needed which detail the successes or failures of the chosen adaptive designs, or alternative designs, in practice. This will inform the literature and provide future stakeholders information about the real-world experiences of seeking regulatory approval and funding, then implementing and conducting ACTs.

In this research, we gained valuable qualitative information about potential challenges and areas of concern that will be relevant to other researchers who are interested in developing adaptive clinical trials. A greater understanding of the adaptive design development process

potentially increases the likelihood of adaptive designs gaining acceptance and approval in the field of academic neurology research in the US and in the broader, global biomedical research community.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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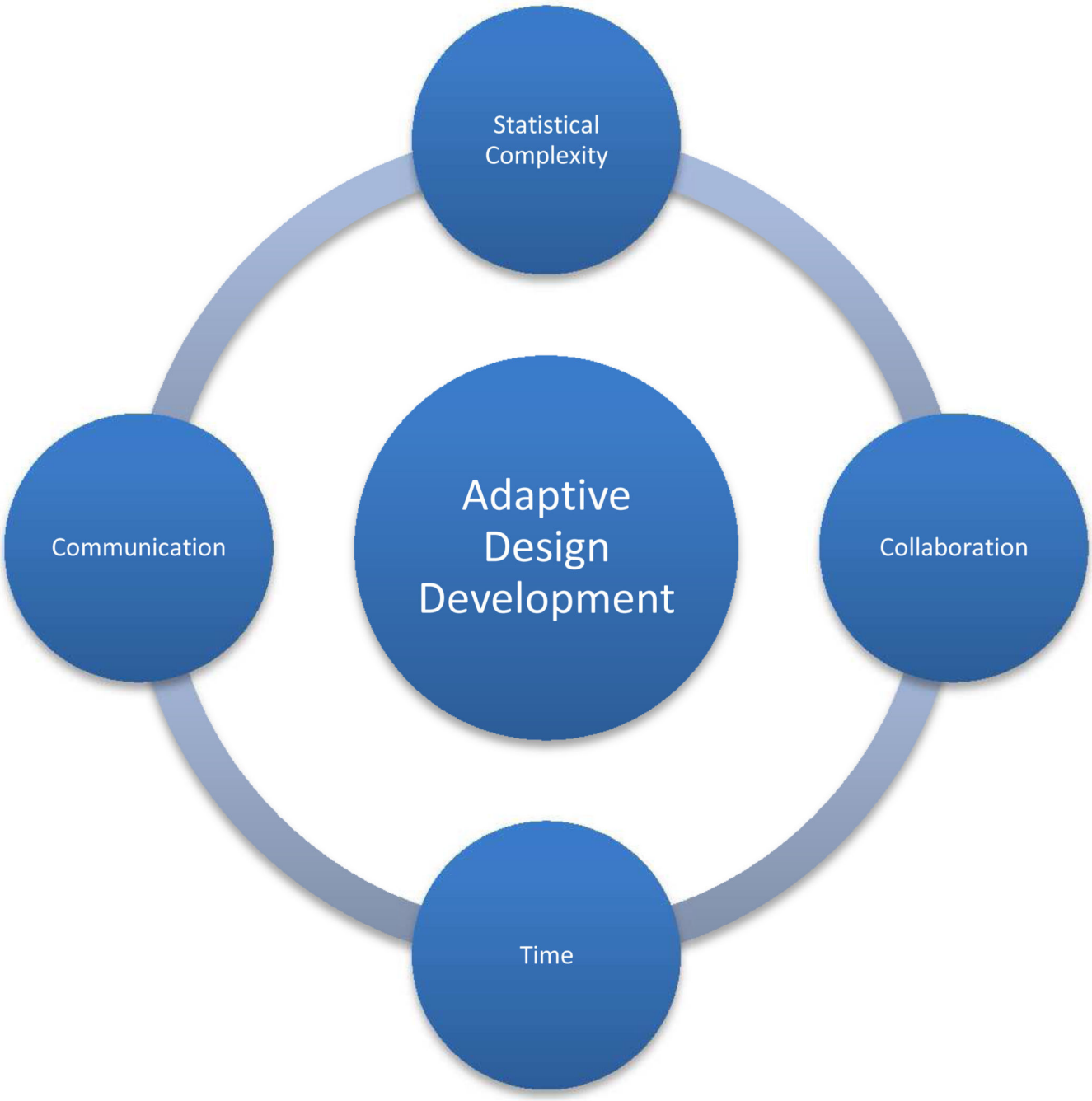

Figure 1.
The Adaptive Design Development Model

Table 1

Participants in ADAPT-IT Face-to-Face meetings

	SHINE	ARCTIC	DCCSCA (now ICECAP)	US-SETT (now ESETT)	ProSPECT
Meeting 1 Dates	**January 19, 2011**	**January 19, 2011**	**July 25, 2011**	**July 14, 2011**	**May 15, 2012**
Stakeholders present	NETT Clinical leaders (3) Adaptive design consultants (4) NETT Academic statisticians (4) SHINE Clinical Team (3) NIH partners (3) FDA partners (0) Mixed methods team (4) Patient advocate (1)	NETT Clinical leaders (2) Adaptive design consultants (6) NETT Academic statisticians (4) ARCTIC Clinical Team (8) NIH partners (3) FDA partners (0) Mixed methods team (4) Patient advocate (1)	NETT Clinical leaders (2) Adaptive design consultants (3) NETT Academic statisticians (4) ICECAP Clinical Team (5) NIH partners (3) FDA partners (5) Mixed methods team (4) Patient advocate (0)	NETT Clinical leaders (2) Adaptive design consultants (3) NETT Academic statisticians (4) ESETT Clinical Team (6) NIH partners (6) FDA partners (3) Mixed methods team (3) Patient advocate (0)	NETT Clinical leaders (2) Adaptive design consultants (6) NETT Academic statisticians (0) ProSPECT Clinical Team (7) NIH partners (1) FDA partners (2) Mixed methods team (3) Patient advocate (0)
Meeting 2 Dates	**July 15, 2011**	**July 26, 2011**	**April 20, 2012**	**May 14, 2012**	**February 25, 2013**
Stakeholders present	NETT Clinical leaders (2) Adaptive design consultants (4) NETT Academic statisticians (5) SHINE Clinical Team (4) NIH partners (3) FDA partners (4) Mixed methods team (4) Patient advocate (1)	NETT Clinical leaders (2) Adaptive design consultants (3) NETT Academic statisticians (5) ARCTIC Clinical Team (4) NIH partners (3) FDA partners (2) Mixed methods team (4) Patient advocate (1)	NETT Clinical leaders (2) Adaptive design consultants (5) NETT Academic statisticians (3) ICECAP Clinical Team (5) NIH partners (5) FDA partners (7) Mixed methods team (3) Patient advocate (1)	NETT Clinical leaders (2) Adaptive design consultants (3) NETT Academic statisticians (4) ESETT Clinical Team (4) NIH partners (2) FDA partners (3) Mixed methods team (4) Patient advocate (0)	NETT Clinical leaders (2) Adaptive design consultants (4) NETT Academic statisticians (3) ProSPECT Clinical Team (3) NIH partners (2) FDA partners (3) Mixed methods team (4) Patient advocate (1)

SHINE: Stroke Hyperglycemia Insulin Network Effort
ARCTIC: Acute Rapid Cooling for Traumatic Injuries of the Cord
DCCSCA: Duration of Cooling in Comatose Survivors of Cardiac Arrest
ICECAP: Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
US-SETT: United States Status Epilepticus Treatment Trial
ESETT: Established Status Epilepticus Treatment Trial
ProSPECT: Progesterone in Acute Stroke
NETT: Neurological Emergencies Treatment Trials