Contemporary Clinical Trials Communications 16 (2019) 100488

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Opinion paper

Creating an academic research organization to efficiently design, conduct, coordinate, and analyze clinical trials: The Center for Clinical Trials & Data Coordination

Kaleab Z. Abebe *, Andrew D. Althouse, Diane Comer, Kyle Holleran, Glory Koerbel, Jason Kojtek, Joseph Weiss, Susan Spillane

Center for Clinical Trials & Data Coordination, Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

ARTICLE INFO

Keywords:
Data coordinating center
Clinical trial management

ABSTRACT

When properly executed, the randomized controlled trial is one of the best vehicles for assessing the effectiveness of one or more interventions. However, numerous challenges may emerge in the areas of study startup, recruitment, data quality, cost, and reporting of results. The use of well-run coordinating centers could help prevent these issues, but very little exists in the literature describing their creation or the guiding principles behind their inception.

The Center for Clinical Trials & Data Coordination (CCDC) was established in 2015 through institutional funds with the intent of 1) providing relevant expertise in clinical trial design, conduct, coordination, and analysis; 2) advancing the careers of clinical investigators and CCDC-affiliated faculty; and 3) obtaining large data coordinating center (DCC) grants. We describe the organizational structure of the CCDC as well as the homegrown clinical trial management system integrating nine crucial elements: electronic data capture, eligibility and randomization, drug and external data tracking, safety reporting, outcome adjudication, data and safety monitoring, statistical analysis and reporting, data sharing, and regulatory compliance.

Lastly, we share numerous lessons that can be taken from our experience. Specifically, we focus on 1) funding for DCCs, 2) the importance of DCCs to clinical researchers, 3) the expertise of DCC personnel, and 4) continually striving to improve.

In conclusion, the CCDC strives to provide high-quality support for the design, conduct, coordination, and analyses of clinical trials, and we hope this paper will serve as a blueprint for future clinical trialists involved in DCCs.

1. Introduction

When properly executed, the randomized controlled trial (RCT) is one of the best vehicles for assessing the effectiveness of one or more interventions. Standardized treatment delivery and outcome assessment, removal of bias due to random allocation, and assessment of harms are just a few of the many advantages over other research designs [1,2]. As a result, many consider the RCT to be the "gold standard" method to evaluate safety and effectiveness of pharmacologic and non-pharmacologic interventions [1,2].

Despite this, numerous challenges may emerge in the areas of study startup, recruitment, data quality, cost, and reporting of results [3–9]. It is well-documented that clinical trials can suffer from delays due to institutional review board (IRB) review, regulatory and non-regulatory approvals, and other oversight committees that are not in sync with one another [3,8,9]. Furthermore, RCTs may experience recruitment issues and subsequently struggle to meet target sample sizes. While estimates vary, approximately 50% of RCTs do not meet their enrollment goals, a number that can be as high as 70% among cancer studies [4,8]. Such issues with approval and recruitment may ultimately lead to unexpected delays and costs, both of which could leave an RCT unfeasible. Further costs can also be accrued by the use of labor-intensive, on-site monitoring to ensure data quality [3,5,8]. This "retrospective" (as opposed to "prospective" or "risk-based") approach to study monitoring

* Corresponding author. Center for Clinical Trials & Data Coordination, Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, 200 Meyran Avenue, Suite 300, Pittsburgh, PA, 15213, USA.
E-mail address: kza3@pitt.edu (K.Z. Abebe).

https://doi.org/10.1016/j.conctc.2019.100488
Received 17 May 2019; Received in revised form 29 October 2019; Accepted 9 November 2019
Available online 12 November 2019

can account for as much as 30% of the total cost, even though there are data to suggest that on-site monitoring doesn't confer additional benefit for data quality [5,6]. Moreover, even if an RCT successfully navigates start-up and data quality issues, its results may never see the light of day. Between 2008 and 2012 only 13% of applicable RCTs reported results to ClinicalTrials.gov within 1 year after study completion, with less than 40% reporting at any time [7].

The problems identified are just a few of the reasons that RCTs should make use of well-run coordinating centers (CCs). By definition, a CC is "a center in the structure of a multicenter trial responsible for coordination of specific activities," [10] such as those related to data collection and analysis as well as treatment administration. Typically, CCs that focus specifically on data collection and analysis are referred to as data coordinating centers (DCCs). There have been efforts to describe best practices for DCCs [11], and there are several descriptions of clinical trial management systems for specific studies [12–15]. However, very little exists in the literature describing the creation of DCCs or the guiding principles behind their inception. Furthermore, what has been published is either disease-specific or localized to a particular study, and therefore difficult to generalize [16–19].

The aims of this paper are multifold. We describe the mission and primary objectives of the University of Pittsburgh Center for Clinical Trials & Data Coordination (CCDC), outline its organizational structure and electronic trial management system, highlight the place of the CCDC in the successful development of clinical trial infrastructure, and provide several "lessons learned" in the creation of a DCC for the benefit of the clinical trials community.

2. Methods

2.1. Objectives of the CCDC

The CCDC was established in late 2015 with generous support through institutional funds provided by the Division of General Internal Medicine at the University of Pittsburgh. From its inception, the Center has aimed to 1) provide relevant expertise in clinical trial design, conduct, coordination, and analysis; 2) advance the careers of clinical investigators and CCDC-affiliated faculty; and 3) successfully obtain large data coordinating center grants.

2.2. Organizational structure

The personnel of the CCDC currently comprises a director (KZA), who is a PhD statistician with more than a decade of experience in clinical trial design, conduct, and analysis; an early-career PhD epidemiologist (AA), two full-time clinical research data coordinators with nearly 40 years of combined experience in clinical research (GK, SS), three systems analysts (KH, JK, JW), and a data analyst (DC). The clinical research data coordinators function as "conduits" between the clinical, data, and statistical teams of each study. They oversee protocol development and training, on-site and centralized study monitoring, safety reporting, and regulatory compliance. The CCDC uses the established statistical analysis and data management infrastructure of the Center for Research on Health Care (CRHC) Data Center, which is also located within the Division of General Internal Medicine and directed by the primary author (KZA). With respect to the requisite number of personnel for a DCC, there are no stated requirements. The number of personnel is dependent on the number of projects, so a DCC must be able to grow as needed to accommodate more demand. With regard to required expertise, hiring personnel to address all aspects of NHLBI's Compendium of Best Practices for Data Coordinating Centers may be a starting point [11].

2.3. Description of the electronic trial management system

The CCDC guides clinical trials from conception to closeout, employing a homegrown system that seamlessly integrates nine crucial elements of clinical trial management including: electronic data capture, eligibility and randomization, drug and external data (i.e., imaging and laboratory sample management) tracking, safety reporting, outcome adjudication, data and safety monitoring, statistical analysis and reporting, data sharing, and regulatory compliance (see Fig. 1).

The choice to develop a homegrown trial management system, as opposed to utilizing a third party package, was determined by the following. First, there are no limits to customization with a homegrown trial management system, while third-party packages may provide only a finite number of features (i.e. only electronic data capture or drug inventory management, but no regulatory document management). Second, the cost of using certain third-party trial management system packages for one or more studies can be prohibitive, while the majority of the cost in a homegrown trial management system is the initial development of the system. Lastly, programs like REDCap are free and provide an application programming interface (API), but there are still limits to how much customization can be done, and RCTs that require CFR Part 11 compliance cannot use REDCap. Below, we describe each element of the trial management system with examples from two ongoing randomized trials for which the CCDC serves as the data coordinating center. The Trial of Administration of Metformin – Autosomal Dominant Polycystic Kidney Disease (TAME-PKD) study is a phase II, double-blind, placebo-controlled, multicenter randomized trial funded by the Department of Defense [20]. Enrollment was completed in December 2018, and 97 adult participants with diagnosed ADPKD and preserved kidney function (i.e., estimated glomerular filtration rate [eGFR] $>$ 60) have been randomized to metformin (maximum titrated dose of 1000 mg per day) or placebo for 24 months. The primary objective is to evaluate the safety and tolerability with key clinical outcomes including total kidney volume (TKV) and eGFR.

The Safety, Tolerability, and Efficacy of Riociguat in Patients with Sickle Cell Disease (STERIO-SCD) trial is also a phase II, double-blinded, placebo-controlled, multicenter randomized trial funded by Bayer Health Care. One hundred participants across at least 11 clinical sites will be randomized to either riociguat (initial dose of 1 mg three times daily) or placebo for 12 weeks. Diagnosis of sickle cell disease and at least 1 of the following high-risk factors serve as primary eligibility criteria: 1) systolic blood pressure $\geq$130 mmHg; 2) urine albumin-to-creatinine ratio of $>$300 mg/g; 3) tricuspid regurgitate velocity $>$2.9

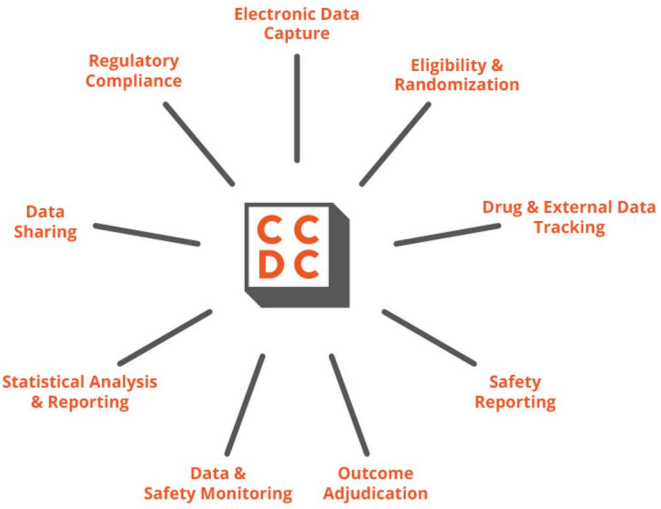

Fig. 1. Clinical trial design elements that are integrated into the CCDC's clinical trial management system: electronic data capture, eligibility and randomization, drug and external data (i.e., imaging and laboratory sample management) tracking, safety reporting, outcome adjudication, data and safety monitoring, statistical analysis and reporting, data sharing, and regulatory compliance.

m/s; 4) NT-proBNP levels ≥160 pg/mL; and 5) urinalysis protein 1 + or greater. Similar to TAME-PKD, the primary objective is to evaluate the safety and tolerability. As of May 2019, 57 participants have been enrolled and randomized.

Electronic data capture. For all CCDC studies, data are directly entered via a password-protected web-based data entry system, which is created using ASP.NET programming and stored using Microsoft SQL Server. All study data collection systems are built to be FDA 21 CFR Part 11 compliant, which mandates certain rules with respect to data access, password protection, audit trails, validation, and direct data entry [21,22]. Each study case report form (eCRF) is developed in conjunction with the clinical study team. In order to ensure that important study forms are not overlooked, eCRFs take into account the categories shown in Table 1. This allows study-agnostic forms (e.g., Withdrawal, AE/SAE forms) to be "recycled" from project to project with very little modification and frees up more time to discuss development of project-specific eCRFs (e.g., a pain scale measure specific to polycystic kidney disease). Additionally, eCRFs are developed to confirm values as they are entered, using required fields, strict data typing, range checking, and pre-defined lists, while limiting the use of free text, to increase the accuracy of the data. For example, adverse events (AEs) are classified by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) or the Medical Dictionary for Regulatory Activities (MedDRA). Also, our web-based system interfaces with RxNorm [23] to ensure that concomitant medications used are recorded uniformly.

Eligibility & randomization. The CCDC utilizes an "eligibility checklist," a dynamically updated web form that is pre-populated with previously entered responses from all questions relating to inclusion/exclusion criteria. Not having a separate, disjointed form with individual checkboxes for each criterion helps to prevent data entry errors that result in ineligible randomizations. Fig. 2 presents a completed "eligibility checklist" for an enrolled participant in the TAME-PKD study.

Drug & external data tracking. The CCDC has experience collaborating with pharmaceutical and drug packaging companies to successfully distribute blinded study drugs for multi-site research studies [24–26]. Through our integrated system, we have the capability to track drug inventory at the level of the central pharmacy, the site pharmacies, and the study participants. This process starts with a "drug portal" that a central pharmacy can interact with to generate unique IDs for a particular unit of the drug (i.e., bottle, blister pack), enter drug-specific information such as dosage and expiration date, and mark for shipment to a particular study site. Next, the individual site pharmacies can log in to the drug portal to mark a shipment as "received" and make the individual units available for release to participants via the relevant case report forms in the web-based data entry system. Third, individual drug units can be destroyed by the central pharmacy and marked in the drug portal due to impending expiration date or return of unused drug by the participants. Finally, because the drug portal provides information about the disposition of each individual drug unit, the DCC and central pharmacy are able to work hand-in-hand to monitor for resupply at the study sites, capture chain-of-custody of the study product, and systematically document study drug accountability across all study sites.

For external data (images, lab samples, procedures, etc.), our process involves eCRFs and core facility facing portals that facilitate the data entry, tracking, and uploading of lab results. We utilize a 3-stage process that is designed to "close the loop" and track each piece of external data from inception to completion. First, the web system generates unique IDs for each sample. Second, sample-specific case report forms are able to be completed by two entities—the study site to document the sample's collection, and the core facility to document its receipt. Third, we provide core facility facing portals to facilitate data entry or upload. This process avoids tedious quality control and allows for real-time monitoring of the disposition of samples throughout the study. Fig. 3 provides an example of how MRI images are managed in the TAME-PKD study.

Safety reporting. As mentioned earlier, all AEs are classified either by CTCAE or MedDRA, rather than utilizing free text data entry that enables non-standardization. Both systems allow individual adverse events to be categorized according to organ system, event term, and grade (for CTCAE) as well as high-level, preferred, and low-level terms (for MedDRA). For heavily regulated studies, an FDA MedWatch form is pre-populated to facilitate reporting of all study-related serious adverse events (SAEs) within necessary reporting timeframes.

Adjudication of outcomes and safety events. The CCDC can facilitate the organization and conduct of adjudication or clinical events committees with the ability to upload supporting documentation (e.g., discharge summaries) to the secure web-based data management system. Fig. 4 provides a schematic of the SAE adjudication process in the STERIO-SCD study. To start, all designated "adjudicators" have access to a portal that displays real-time information on each outstanding safety event. The primary and secondary adjudicators can view uploaded hospital discharge summaries as well as complete their assessment on the adjudication form. Once both adjudicators have finished, they are notified via email if any discrepancies are present and are provided the opportunity to review them and discuss. Only after a conclusion is reached can the primary adjudicator finalize the event.

Data & safety monitoring. The CCDC works with the clinical investigators to develop and formalize a comprehensive, risk-based data and safety monitoring plan for each study which will include specifics for a site initiation visit, interim monitoring visits, for-cause visits (if necessary), and a close-out visit. Our risk-based monitoring plan is based on recent FDA guidance [27] that focuses on 1) eligibility confirmation, so that all site PIs will be able to review all screening-related CRFs and electronically sign prior to randomization; 2) consent monitoring, enabling all clinical sites to upload signed participant consents to a secure repository, which the data coordinator will be able to monitor in real time; 3) complete ascertainment of primary and key secondary outcomes, to the extent that the data coordinator will be notified in real time if there are instances of missing outcomes, which will allow the coordinator to query the clinical site and resolve the issue; 4) serious adverse events and protocol violations, such that the data coordinator is notified of all SAEs and protocol violations as they occur.

Table 1

eCRFs			
Series	#	Form	Assessment periods
A: Screening & Baseline	0	Eligibility Checklist	Screen
	3	Demographics	Screen
	5	Screening History	Screen
B: Follow up Visits	4	Vitals	Screen-Baseline-Follow Up
	7	Labs	Screen-Baseline-Follow Up
	8	Medical History	Screen-Baseline-Follow Up
	9	AE Review of Symptoms	Baseline-Follow Up
	10	Physical	Screen-Baseline-Follow Up
C: External Tests & Procedures	15	Echocardiogram	Baseline-Follow Up
	14	MRI	Baseline-Follow Up
		Sample Collection	Screen-Baseline-Follow Up
D: Standardized Measures & Clinical Outcomes		Surveys	Baseline-Follow Up
E: Adherence to Study Intervention	13	Study Drug	Baseline-Follow Up
F: Adverse Experiences	30	AE/SAE	As Needed
	31	Pregnancy	As Needed
	32	Hospitalization	As Needed
G: Concomitant Medication	6	Concomitant Medications	Screen-Baseline-Follow Up
H: Subject Follow Up & Vital Status	33	Death Notification	As Needed
	34	Unmasking Drug	As Needed
	35	Protocol Deviation	As Needed
	36	Withdrawal	As Needed

TAME SCREENING ELIGIBILITY CHECKLIST for Tufts-001

Home Page >>WebForms Portal >>Search Participants >>INC/EXC Checklist

If any of the following inclusion criteria are answered no, the patient is ineligible for enrollment into the study.

Inclusion Criteria	Yes/No	Form Involved
1. Autosomal Dominant Polycystic Kidney Disease	Yes	Form 4-Clinical History
2. Signed Informed Consent	Yes	Form 3-Demographic
3. Age 18-60	Yes	Form 3-Demographic
4. Fluent English speaking	Yes	Form 3-Demographic

If any of the following exclusion criteria are answered yes, the patient is ineligible for enrollment into the study.

Exclusion Criteria	Yes/No	Form Involved
1. Active military personnel	No	Form 3-Demographic
2. Current participation in a clinical trial with a study medication	No	Form 3-Demographic
3. Estimated GFR<60 cc/min/1.73m2	No	Form 10-Labwork
4. Diabetes	No	Form 10-Labwork Form 4-Clinical History
5. Systemic disease, other than hypertension and PKD	No	Form 4-Clinical History
6. A solitary kidney	No	Form 4-Clinical History
7. Allergy/intolerance to metformin	No	Form 4-Clinical History
8. Pregnant or lactating or intending to become pregnant within the next 3 years?	No	Form 4-Clinical History
9. Unstable or unclipped cerebral aneurysm	No	Form 4-Clinical History
10. Active Coronary Artery Disease	No	Form 4-Clinical History
11. MRI incompatible device/implant	No	Form 4-Clinical History
12. Severe Claustrophobia	No	Form 4-Clinical History
13. Any solid organ transplant	No	Form 4-Clinical History
14. History of non-compliance	No	Form 4-Clinical History
15. Vitamin B12 deficiency	No	Form 10-Labwork
16. Use of any medication(s) that may interact with metformin	No	Form 9-Review of Medications

Is patient eligible to participate?

Yes No Pending

Please answer the following questions

BP satisfactory (Form 7 #3)(Systolic:120 Diastolic:67)
EKG (Form 7 #5)

Fig. 2. The TAME-PKD study involved 20 inclusion and exclusion criteria across 4 forms administered at screening. The layout of the "eligibility checklist" allows study coordinators to see a particular participant's status (eligible, ineligible, or pending) as well as the particular form from which the criteria originates.

The CCDC works with the clinical team to define and implement "protocol alerts" for each study. This would include email notifications for situations in which a participant meets enrollment criteria, a form or set of forms needs to be electronically signed by the site investigator, a serious adverse event or protocol deviation report is submitted, or a safety issue such as death arises.

Additionally, we work to ensure that study personnel receive the appropriate electronic data capture training. These efforts will focus on ensuring that clinical site personnel have appropriate familiarity with the details of the study manual of procedures (MOP) and other study-related documents, all of which are posted to the study-specific web page and updated as needed. The CCDC will hold on-site or virtual training and certification meetings (as well as ongoing virtual training for new study personnel as needed), at which staff from each of the clinical sites will be trained on the use of the electronic system for data management.

Statistical analysis & reporting. The CCDC uses a standard report template that is adapted to the specifics of each study. This serves as the basis for monthly reports as well as data and safety monitoring board (DSMB) open session reports. The process of disseminating study results begins well before the last study participant completes follow-up. Approximately 6 months prior to study completion, the statisticians work on finalizing the analytic programs and datasets that will be used to conduct the primary analyses according to the study statistical analysis plan (SAP). The CCDC works with the investigative team to create a writing team that begins to draft sections of the primary manuscript, including blank shell tables and figures. These are circulated (without data) to the larger investigative team and approved prior to the end of participant follow-up. Once the last participant completes study follow-up, the Data Center statisticians fill in the shell tables and figures and circulate to the writing team for submission to a journal. The CCDC works with study investigators to ensure that the results of the proposed study are reported using the CONSORT guidelines [28], and disseminated in a timely fashion.

Data sharing. The CCDC assists with registration, updates, and final reporting to clinicaltrials.gov. We also facilitate end-of-study data sharing by maintaining complete sets of data dictionaries, including format libraries, macro libraries, and other tools needed to rapidly and accurately analyze data quality and to share data with the NIH Repositories such as NHLBI's BioLINCC and NIDDK's Central Data Repository.

Regulatory compliance. Finally, the CCDC is set up to handle the regulatory aspects of clinical trials. We utilize an electronic Master Regulatory File (eMRF) that is in keeping with the International Conference on Harmonisation (ICH) E6: Good Clinical Practice Guideline. The eMRF provides 1) a secure, web-based system to facilitate document submission and retrieval, 2) automated email alerts indicating pending expiration of essential documents, 3) a platform to facilitate electronic signatures on key documents, and 4) the ability to track and disseminate regulatory documents within and between institutional review boards. Each of the sites will be able to upload to the eMRF and view site- and participant-level documents specific to their site. In addition, they will be able to view shared documents such as the study protocol, MOP, and case report forms. Fig. 5 provides examples of several web-based forms

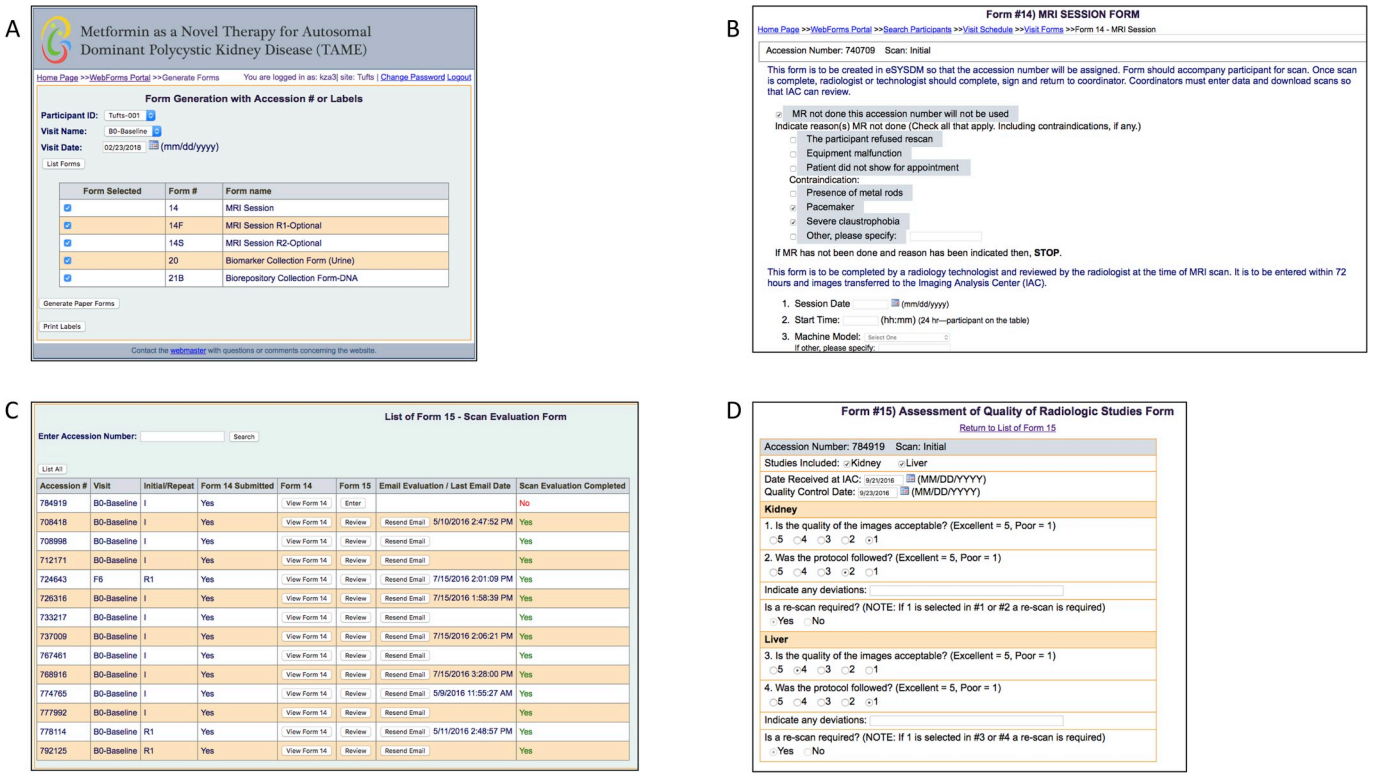

Fig. 3. An example of how the clinical trial management system manages MRI images within the TAME-PKD study. (a) The study team generates unique accession numbers for each image. (b) An MRI-specific case report form is completed with information as to whether a scan was completed as well as specifics of the scan. (c) The core facility in charge of centrally reviewing the images is notified that an image is available for review. (d) The core facility reviews the uploaded image and completes the associated case report form.

that feed information into the eMRF.

3. Results

Overview. As of the end of 2018, the CCDC has been in existence for just over 3 years and has much to show for it. We currently serve as the data coordinating center for four clinical trials (TAME-PKD, STERIO-SCD, VWDMin, and FAM-ACT), which vary in size and scope. The TAME-PKD and STERIO-SCD studies have already been described—the former having recently completed enrollment in December 2018. The Minimize Menorrhagia in Women with Type I Von Willebrand Disease (VWDMin) is an NHLBI-funded phase III multicenter, crossover trial which plans to enroll sixty women (18–45 years of age) across 19 clinical sites with mild-to-moderate VWD and menorrhagia. The primary objective is to compare recombinant von Willebrand factor to tranexamic acid. The Family Partners for Health Action (FAM-ACT) study is an NIDDK-funded parallel arm randomized trial that aims to compare the effectiveness of a novel diabetes education program versus individual patient-focused diabetes self-management education and care management (I-DSME/CM) in improving patients' diabetes-related health outcomes, self-management behaviors, perceived social support for diabetes, and perceived autonomy support from family. Two hundred sixty-eight patients with type 2 diabetes and either poor glycemic or blood pressure control, together with a family supporter for each, will be randomized to receive the novel diabetes education program or more traditional Community Health Worker (CHW)-led, individually focused DSME/CM.

Lessons Learned. There are numerous lessons that the CCDC can take from the experience thus far and impart to researchers who plan to develop data coordinating centers in the future. The first and most obvious lesson is that it is very difficult to obtain funding to develop coordinating center infrastructure. The primary funding agency for biomedical research in the US, the National Institutes of Health (NIH), provides funding based either on the scientific area (e.g., opioid use or for diabetes) or on the career stage of the applicant (e.g., K23 career development award, R01 independent investigator award). On the other hand, there are numerous funding announcements for clinical research consortiums or clinical trial networks, though priority consideration is typically given to applicants that are ready at the beginning of funding, as opposed to an applicant with a solid concept but with little structure already in place. The CCDC was fortunate to have a supportive department and division that had the foresight to see how having a data coordinating center infrastructure would be beneficial to future research. This "institutional investment" is critical to the sustainability of DCCs, especially given the cyclical nature of grant funding. At the very least, institutions should provide a base level of effort to cover critical personnel. The return-on-investment is high because, once established, DCCs be can self-sustaining with numerous and recurrent projects.

The second lesson is that it is often difficult to convince clinical researchers of the need for a DCC, especially if what they've done previously has "worked." The CCDC has been successful in this regard because we underscore how our process complements the clinical coordinating center, thus allowing them more time to focus on the protocol- and regulatory-specific tasks. Since many clinical trial–specific funding announcements now require separate proposals for clinical and data coordinating centers, establishing the necessity of a DCC is admittedly becoming easier.

Third, the CCDC has been extremely fortunate to have data coordinators with decades of past experience as health professionals that informs their roles on the data coordinating side of clinical trials. While this is not a necessary requirement for personnel, it is sufficient in the opinion of the authors. There are numerous examples across the 4 RCTs previously mentioned where this experience has enhanced electronic

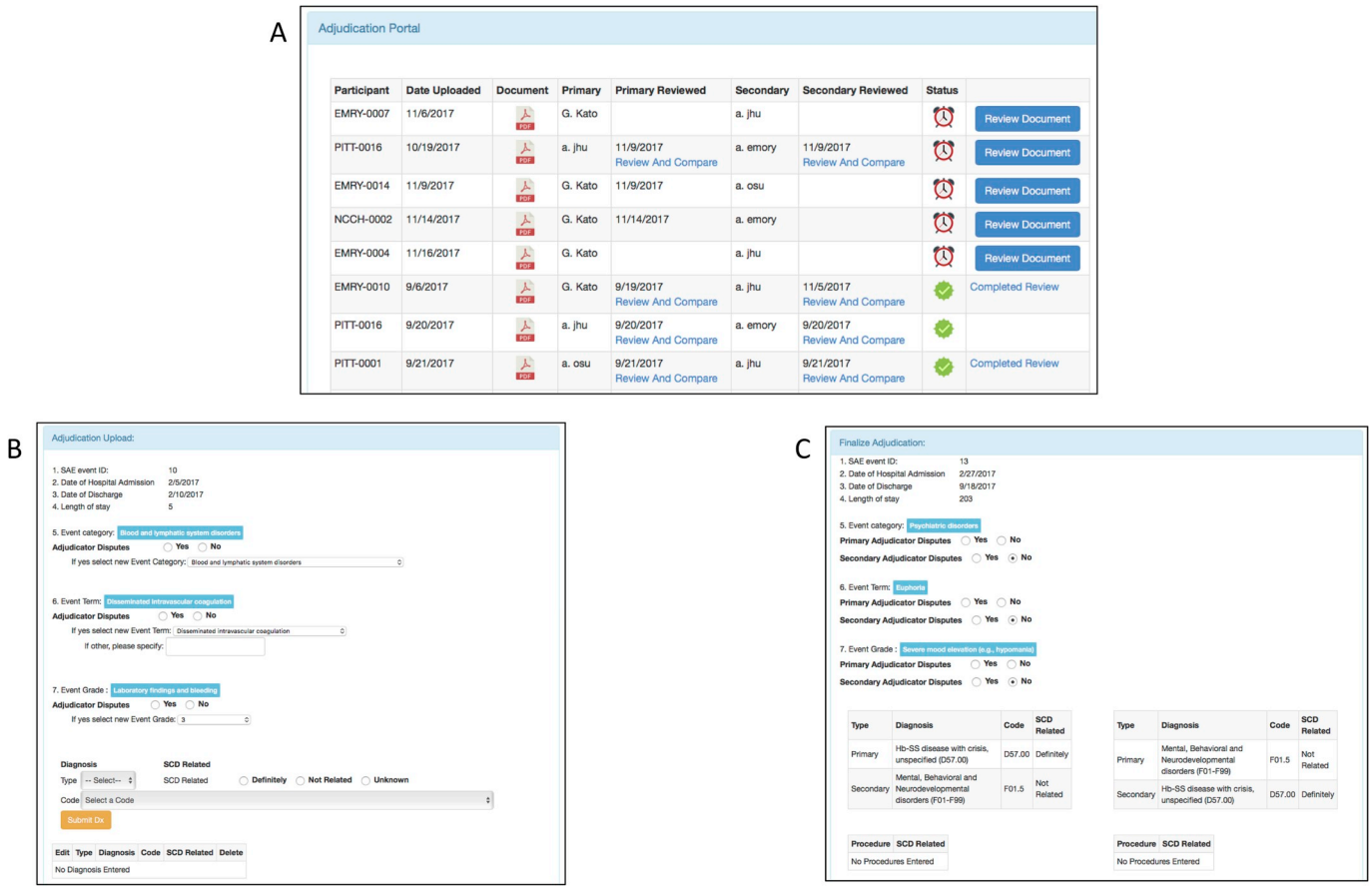

Fig. 4. An example of the adjudication process for serious adverse events in the STERIO-SCD study. (a) The primary and secondary adjudicator are able to see the status of each SAE that have been assigned to along with the relevant hospital discharge summary to review. (b) Each adjudicator completes a case report form with their assessment of the SAE. (c) The assessments of both adjudicators are compared, and if discrepancies exist, they are reconciled prior to a final determination.

case report form development, safety data collection and reporting, and data monitoring. In the absence of past clinical experience, finding DCC personnel that have relevant certifications (e.g., certified clinical research coordinator) is also helpful.

The last lesson revolves around the need to continually improve our clinical trial management system. As a result, we always strive to learn from past experiences and improve accordingly. The challenge is knowing how best and when to implement any improvements or modifications; for example, should they be applied globally, to all current and future RCTs, or should they be implemented solely for the RCT in which the problem originated? The CCDC attempts to strike a balance between the two by devoting bi-weekly meetings to the discussion of the trial management system. Issues are brought up at these meetings and we decide the best way to implement the proposed solutions.

4. Discussion

The University of Pittsburgh Center for Clinical Trials & Data Coordination strives to be a national leader in the design, conduct, coordination, and analyses of clinical trials. The CCDC has developed a process in which data coordinators serve as conduits between the clinical, statistical analysis, and data management teams. In combination with a home-grown electronic trial management system, this allows for a streamlined and standardized approach to tackling the critical elements of trial coordination. Additionally, this alleviates the ever-growing burden on the clinical side of the study (particularly for lead clinical study coordinators), thereby preventing delays in study start-up and conduct and facilitating more timely data analysis, publication, and data sharing. While the approach described above to creating the CCDC reflects the authors experience, it is by no means a singular and exhaustive method to developing a DCC. As stated above, though multiple successful DCCs exist, there are few detailed descriptions of their development and structure, which limited our ability to describe our own CCDC in the context of others. We believe that publication of reports such as this one, sharing how academic DCCs have developed their infrastructure, will allow readers to compare and learn from various approaches.

The mission of the CCDC is congruent with that of the National Institutes of Health, which has undertaken concerted efforts to "improve the quality and efficiency of clinical trials." As Hudson et al. articulated in a 2016 Viewpoint in *JAMA*, the NIH has initiated reforms to key points along a clinical trial's "lifespan." [9] Each of the reforms—from the requirement of Good Clinical Practice (GCP) training for all investigators and staff, to the foregrounding of clinical trial-specific funding announcements, and the emphasis on early registration with the ClinicalTrials.gov database—integrates well with the primary goals of the CCDC.

While the effort by the NIH to overhaul the nation's clinical trials infrastructure appears to be the logical next step, there is more that can be done. The US could look to the UK as a model for a more connected clinical trials infrastructure [29]. As of this writing, 46 UK clinical trials units have been registered, all of which meet a set of minimum standards in four main competencies: 1) expertise, continuity, and stability; 2) quality assurance; 3) information systems; and 4) statistical input [30]. One could imagine numerous DCCs and/or academic research organizations in the US that adhere to a minimum set of guidelines, possibly based on recent best practices from the National Heart, Lung, and Blood Institute [11]. The Trial Innovation Network, sponsored by the National

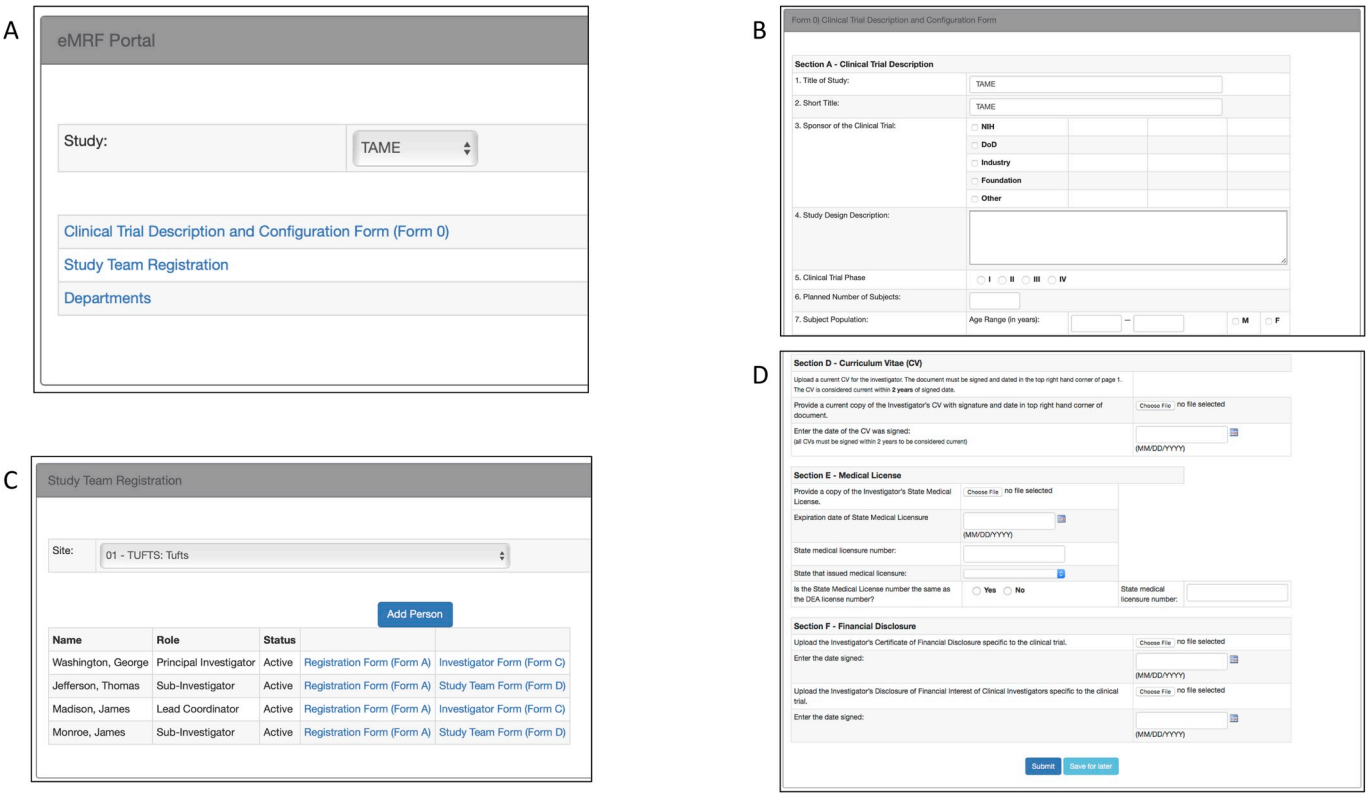

Fig. 5. An example of content collected within the eMRF. (a) Multiple clinical trials can be managed with study personnel and department information shared across trials as needed. (b) A sample of information collected describing each clinical trial. (c) Within a clinical trial study site, study personnel can be added. (d) A sample of information collected at the level of study personnel.

Center for Advancing Translational Sciences (NCATS), is a step in the right direction. The Network is composed of 3 Trial Innovation Centers (TICs) and a Recruitment Innovation Center (RIC), whose goals are to help researchers overcome roadblocks in clinical trials by focusing on innovative approaches in operations and collaboration [31]. However, the focus of the TICs seems to be on clinical trial start-up and regulatory issues, such as single IRBs and initiation of master agreements, rather than on developing a data coordinating center infrastructure.

In conclusion, there is a major demand for the development of clinical trials infrastructure, specifically data coordinating centers. We have outlined our experience and process as well as provided some "lessons learned" for the development of future data coordinating centers. We hope this paper will serve as a blueprint for future clinical trialists involved in DCCs.

Funding

The featured studies were supported by funding from the Department of Defense (W81XH-15-1-0663, PI: Kyongtae Bae), the Bayer Corporation (PI: Greg Kato). The funding for the development of the CCDC was provided through institutional funds. The authors have no other conflicts of interest to disclose.

Acknowledgements

The authors would like to acknowledge Dr. Wishwa Kapoor, former chief of the Division of General Internal Medicine, for his unwavering support (both professionally and fiscally) of the Center for Clinical Trials & Data Coordination. Additionally, we appreciate the editorial assistance from Ethan Lennox, who is the medical editor in the Division of General Internal Medicine.

References

[1] L. Friedman, C. Furberg, D. DeMets, D.M. Reboussin, C.B. Granger, Fundamentals of Clinical Trials, fifth ed., Springer, Basel, Switzerland, 2015.
[2] S. Evans, N. Ting, Fundamental Concepts for New Clinical Trialists, Chapman and Hall/CRC Biostatistics Series, Boca Raton, FL, 2015, https://doi.org/10.1201/b19777.
[3] C. Reith, M. Landray, P.J. Devereaux, J. Bosch, C.B. Granger, C. Baigent, R. M. Califf, R. Collins, S. Yusuf, Randomized clinical trials — removing unnecessary obstacles, N. Engl. J. Med. 369 (2013) 1061–1065, https://doi.org/10.1056/NEJMsb1300760.
[4] S. Treweek, M. Pitkethly, J. Cook, C. Fraser, E. Mitchell, F. Sullivan, C. Jackson, T. K. Taskila, H. Gardner, Strategies to improve recruitment to randomised trials, Cochrane Database Syst. Rev. (2018), https://doi.org/10.1002/14651858.MR000013.pub6.
[5] D. Venet, E. Doffagne, T. Burzykowski, F. Beckers, Y. Tellier, E. Genevois-Marlin, U. Becker, V. Bee, V. Wilson, C. Legrand, M. Buyse, A statistical approach to central monitoring of data quality in clinical trials, Clin. Trials 9 (2012) 705–713, https://doi.org/10.1177/1740774512447898.
[6] A.A. Kirkwood, T. Cox, A. Hackshaw, Application of methods for central statistical monitoring in clinical trials, Clin. Trials 10 (2013) 783–806, https://doi.org/10.1177/1740774513494504.
[7] M.L. Anderson, K. Chiswell, E.D. Peterson, A. Tasneem, J. Topping, R.M. Califf, Compliance with results reporting at ClinicalTrials.gov, N. Engl. J. Med. 372 (2015) 1031–1039, https://doi.org/10.1056/NEJMsa1409364.
[8] A.J. Vickers, Clinical trials in crisis: four simple methodologic fixes, Clin. Trials 11 (2014) 615–621, https://doi.org/10.1177/1740774514553681.
[9] K.L. Hudson, M.S. Lauer, F.S. Collins, K. JM, H. KL, C. R, W. TH, Z. DA, Toward a new era of trust and transparency in clinical trials, J. Am. Med. Assoc. 316 (2016), https://doi.org/10.1001/jama.2016.14668, 1353.
[10] C.L. Meinert, Clinical Trials : Design, Conduct, and Analysis, Oxford University Press, 2012. https://global.oup.com/academic/product/clinicaltrials-9780195387889#.WS7Z0rmK8c8.mendeley&title=ClinicalTrials&description=First. (Accessed 31 May 2017). published in 1986, this landmark text is the definitive guide to clinical trials, written by one of the leading experts in th.
[11] Data Coordinating Centers' Best Practices. https://www.nhlbi.nih.gov/research/reports/2011-data-coordinating-centers, 2011.
[12] W. Zhao, V. Durkalski, K. Pauls, C. Dillon, J. Kim, D. Kolk, R. Silbergleit, V. Stevenson, Y. Palesch, An electronic regulatory document management system for a clinical trial network, Contemp. Clin. Trials 31 (2010) 27–33, https://doi.org/10.1016/j.cct.2009.09.005.

[13] W. Zhao, K. Pauls, Architecture design of a generic centralized adjudication module integrated in a web-based clinical trial management system, Clin. Trials (2015) 1–11, https://doi.org/10.1177/1740774515611889.
[14] W. Zhao, B.D. Waldman, C. Dillon, K. Pauls, J. Kim, L. Patterson, M.D. Ginsberg, M. D. Hill, Y. Palesch, A web-based medical safety reporting system for a large multicenter clinical trial: the ALIAS experience, Contemp. Clin. Trials 31 (2010) 536–543, https://doi.org/10.1016/j.cct.2010.08.010.
[15] V. Durkalski, Wenle Zhao, C. Dillon, J. Kim, A web-based clinical trial management system for a sham-controlled multicenter clinical trial in depression, Clin. Trials 7 (2010) 174–182, https://doi.org/10.1177/1740774509358748.
[16] B. Rolland, B.R. Smith, J.D. Potter, Coordinating centers in cancer epidemiology research: the asia cohort consortium coordinating center, cancer epidemiol, Biomark. Prev. 20 (2011) 2115–2119, https://doi.org/10.1158/1055-9965.EPI-11-0391.
[17] B.W. Campbell-Jenkins, C.C. Addison, L. Young, P. Anugu, G. Wilson, D. Sarpong, Development of the Jackson heart study coordinating center, Int. J. Environ. Res. Public Health 6 (2009) 1597–1608, https://doi.org/10.3390/ijerph6051597.
[18] I.T. Croghan, S.D. Viker, A.H. Limper, T.K. Evans, A.R. Cornell, J.O. Ebbert, M. A. Gertz, Developing a clinical trial unit to advance research in an academic institution, Contemp. Clin. Trials 45 (2015) 270–276, https://doi.org/10.1016/j.cct.2015.10.001.
[19] S.R. Brown, D. Sherratt, G. Booth, J. Brown, F. Collinson, W. Gregory, L. Flanagan, Experiences of establishing an academic early phase clinical trials unit, Clin. Trials (2017), https://doi.org/10.1177/1740774517710250, 1740774517771025.
[20] S.L. Seliger, K.Z. Abebe, K.R. Hallows, D.C. Miskulin, R.D. Perrone, T. Watnick, K. T. Bae, A randomized clinical trial of metformin to treat autosomal dominant polycystic kidney disease, Am. J. Nephrol. (2018), https://doi.org/10.1159/000488807.
[21] E. Tawil, H. Hagras, An adaptive genetic-based incremental architecture for the on-line coordination of embedded agents, Cognit. Comput. 1 (2009) 300–326, https://doi.org/10.1007/s12559-009-9022-y.
[22] U.S.F. and D. Administration, Guide for Industry - Computerized Systems Used in Clinical Investigations, MD US Dep. Heal. Drugs, Rockville, 2007, pp. 1–9. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf. (Accessed 31 October 2018). http://www.fda.gov/cder/guidance/index.htmorhttp://www.fda.gov/cber/guidelines.htm.
[23] Bethesda (MD), US national library of medicine, RxNorm (2016) [Internet].
[24] R.W. Schrier, K.Z. Abebe, R.D. Perrone, V.E. Torres, W.E. Braun, T.I. Steinman, F. T. Winklhofer, G. Brosnahan, P.G. Czarnecki, M.C. Hogan, D.C. Miskulin, F. F. Rahbari-Oskoui, J.J. Grantham, P.C. Harris, M.F. Flessner, K.T. Bae, C.G. Moore, A.B. Chapman, Blood pressure in early autosomal dominant polycystic kidney disease, N. Engl. J. Med. 2014 (2014) 2255–2266, https://doi.org/10.1056/NEJMoa1402685.
[25] V.E. Torres, K.Z. Abebe, A.B. Chapman, R.W. Schrier, W.E. Braun, T.I. Steinman, F. T. Winklhofer, G. Brosnahan, P.G. Czarnecki, M.C. Hogan, D.C. Miskulin, F. F. Rahbari-Oskoui, J.J. Grantham, P.C. Harris, M.F. Flessner, C.G. Moore, R. D. Perrone, others, Angiotensin blockade in late autosomal dominant polycystic kidney disease., N. Engl, J. Med. 371 (2014) 2267–2276, https://doi.org/10.1056/NEJMoa1402686.
[26] C.G. Moore, S. Spillane, G. Simon, B. Maxwell, F.F. Rahbari-Oskoui, W.E. Braun, A. B. Chapman, R.W. Schrier, V.E. Torres, R.D. Perrone, T.I. Steinman, G. Brosnahan, P.G. Czarnecki, P.C. Harris, D.C. Miskulin, M.F. Flessner, K.T. Bae, K.Z. Abebe, M. C. Hogan, Closeout of the HALT-PKD trials, Contemp. Clin. Trials 44 (2015) 48–55, https://doi.org/10.1016/j.cct.2015.07.017.
[27] U.S Food and Drug Administration, Guidance For Industry: Oversight Of Clinical Investigations — A Risk-Based Approach To Monitoring, 2013, pp. 1–19. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf.
[28] K.F. Schulz, D.G. Altman, D. Moher, CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials, Ann. Intern. Med. 152 (2010) 726–732, https://doi.org/10.7326/0003-4819-152-11-201006010-00232.
[29] E. McFadden, S. Bashir, S. Canham, J. Darbyshire, P. Davidson, S. Day, S. Emery, J. Pater, S. Rudkin, M. Stead, J. Brown, The impact of registration of clinical trials units: the UK experience, Clin. Trials 12 (2014) 166–173, https://doi.org/10.1177/1740774514561242.
[30] UK Clinical Research Collaboration Registered Clinical Trials Unit Network (n.d.), https://www.ukcrc-ctu.org.uk/. (Accessed 9 January 2019).
[31] National Center for Advancing Translational Sciences, Trial innovation network, 2018. https://ncats.nih.gov/ctsa/projects/network. (Accessed 9 January 2019).