Contemporary Clinical Trials Communications 8 (2017) 114–121

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

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

Review article

Use of a single, independent IRB: Case study of an NIH funded consortium

Brandy Stoffel[a,*], Christine Sorkness[b], Carol Pech[c]

[a] Inner-City Asthma Consortium, University of Wisconsin-Madison, 800 University Bay Dr., Suite 105, Madison, WI 53705, United States
[b] Pharmacy and Medicine, Institute for Clinical and Translational Research, and Inner-City Asthma Consortium, University of Wisconsin-Madison, United States
[c] Health Sciences IRBs, University of Wisconsin-Madison, United States

ARTICLE INFO

Keywords:
Single IRB
Consortium
Multi-site studies
Independent IRB
NIH policy

ABSTRACT

In 2014, the Request for Applications from the National Institutes of Health. (NIH) for continued funding of a multi-site clinical and mechanistic research. Network, Inner City Asthma Consortium (ICAC), called for "efficient IRB review. And approval for multi-center studies" and "IRB approval within 30 days from. Submission". These requirements were precursors to the NIH policy of single. IRB review for multi-site studies. Here we share our challenges, implementation processes, results, and recommendations, using a single, independent IRB.

1. Introduction and Inner City Asthma Consortium history

In June of 2016, the National Institutes of Health released a final policy on the use of a single Institutional Review Board (IRB) [1] for multi-site research with the goal to enhance and streamline the IRB review process in the context of multi-site research. With the release of this final policy, institutions and researchers are looking for examples of how to implement logistics, and metrics of the time necessary to establish new policies, procedures, and agreements. This is a review of the Inner-City Asthma Consortium's pathways to, and experiences with, a single IRB to date.

The National Institute of Allergy and Infectious Diseases (NIAID) established a series of three programs to establish research networks to study asthma in inner city children: the National Cooperative Inner City Asthma Study (NCICAS, 1991–1997); Inner City Asthma Study (ICAS, 1994–2001; and Inner City Asthma Consortium (ICAC1, 2002–2009, and ICAC2 2009–2014).[2] These networks have included asthma specialists, study coordinators, and research teams located within academic health centers in large urban locations across the U.S., as well as a Statistical and Clinical Coordinating Center at Rho, Inc. And a NIAID-appointed Data Safety and Monitoring Committee. Beginning in 2002, the ICAC Scientific Coordination and Administrative Center (SCAC) was established, and housed at the University of Wisconsin-Madison (UW). UW is responsible for the overall scientific leadership and administrative functions of ICAC, including fiscal management of the clinical and mechanistic site subcontracts.

In 2013, the Funding Opportunity Announcement (FOA) for ICAC3 was issued, utilizing a UM1 Multi-Component Research Project Cooperative Agreement mechanism. For the first time, ICAC leadership was faced with the FOA requirement to "establish a plan for efficient IRB review (within 30 calendar days from submission) and approval for multi-center studies using federated IRB models", to replace the existing process of protocol approval at its multiple, independent, academic IRBs. After extensive deliberations and conference calls with each of the ten clinical site investigators and regulatory officials, the ICAC Steering Committee agreed to select Western IRB (WIRB) as its single IRB. Considerations for this selection included: AAHRPP accreditation status; UW's experience and contract with WIRB (as of 2008) for review of the majority of industry-sponsored research; WIRBs performance at UW with timely reviews and attentive interactions; and WIRB's regulatory expertise to deal with state laws unique to ten ICAC sites. UW's grant for ICAC3 was successfully funded in July 2014, and its budget included an IRB Facilitator position to implement our proposed single IRB model.(See Fig. 1).

2. Methods and design (timeline reference September–december 2014)

Upon hire, the IRB Facilitator and the UW ICAC3 SCAC Assistant Director participated in introductory teleconferences with each ICAC3 clinical site lead investigator to discuss expectations and timelines. Conference calls with representatives of ICAC's Statistical and Clinical Coordinating Center (Rho,Inc.) and the NIAID ICAC3 program managers followed, to clarify roles and responsibilities in implementing the single IRB process. Finally, a series of conference calls were held between WIRB, IRB Facilitator, and ICAC3 administration, to discuss the process for protocol submission and review, including local site reviews.

* Corresponding author.
E-mail addresses: bstoffel@medicine.wisc.edu (B. Stoffel), casorkness@medicine.wisc.edu (C. Sorkness), cap@medicine.wisc.edu (C. Pech).

http://dx.doi.org/10.1016/j.conctc.2017.09.001
Received 9 March 2017; Received in revised form 24 August 2017; Accepted 5 September 2017
Available online 06 September 2017

Acronym

FDA	Federal Drug Administration
FOA	Funding Opportunity Announcement
FWA	Federal Wide Assurance
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
ICAC	Inner City Asthma Consortium
ICAC1	Inner City Asthma Consortium grant funding period 2002–2009
ICAC2	Inner City Asthma Consortium grant funding period 2009–2014
ICAC3	Inner City Asthma Consortium grant funding period 2014-present
IRB	Institutional Review Board
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PPD	Pharmaceutical Product Development, LLC
SCAC	Scientific Coordination and Administrative Center
WIRB	Western Institutional Review Board

During these calls, participants from all areas raised many questions regarding the details of the IRB submission process as well as the effort required to implement a single IRB process across all ICAC3 sites. For example, would the IRB Facilitator submit all protocol-level reviews, local site applications, protocol- and site-level changes in research, continuing reviews, and reportable events? Or would local ICAC3 coordinators be responsible for all site submissions? The ICAC3 SCAC decided that, initially, the IRB Facilitator would conduct all submissions, with the eventual goal of having site specific submissions managed by site coordinators.

After finalizing the single IRB process and roles, the IRB Facilitator scheduled calls with each of the ICAC site's designated regulatory officials/IRB administrators to review the proposed ICAC single IRB process and to gather site-specific institutional requirements. With WIRB agreeing to make consent documents "site specific" by incorporating locally-required language into the approved consent template, the IRB Facilitator needed to prospectively collect the required consent language from each site.

The following is an annotated list of questions directed to each site IRB administrator:

1. Do you currently work with Western IRB?
   a. If so, do you have a consent template arranged?

This question had two purposes: First, if a site had a consent template already developed for ceded IRB reviews, this likely could identify required site language for ICAC studies. Second, site IRB administrators were informed that regardless of any site affiliations and previously arranged consent language with WIRB, the NIH consent template would be required for all ICAC site reviews by WIRB.

   b. What is your current institutional signoff for studies that are ceded to WIRB?

2. **What are your site's needs for documenting compliance with institutional requirements and policies** (e.g. Clinical Research Unit/Clinical Research Center, Investigational Pharmacy, Conflict of Interest)**?**
   a. Relying Site Requirements Checklist

The IRB Facilitator asked each site if a "Relying Site Requirements Checklist" would be useful. This checklist would allow site coordinators to document that standard institutional requirements common to all sites were met; an "other" section was also included to account for any unique requirements for a particular site. Most sites rejected the idea of using such a checklist since most had their own mechanism for documenting institutional requirements (e.g., via an electronic system or paper checklist).

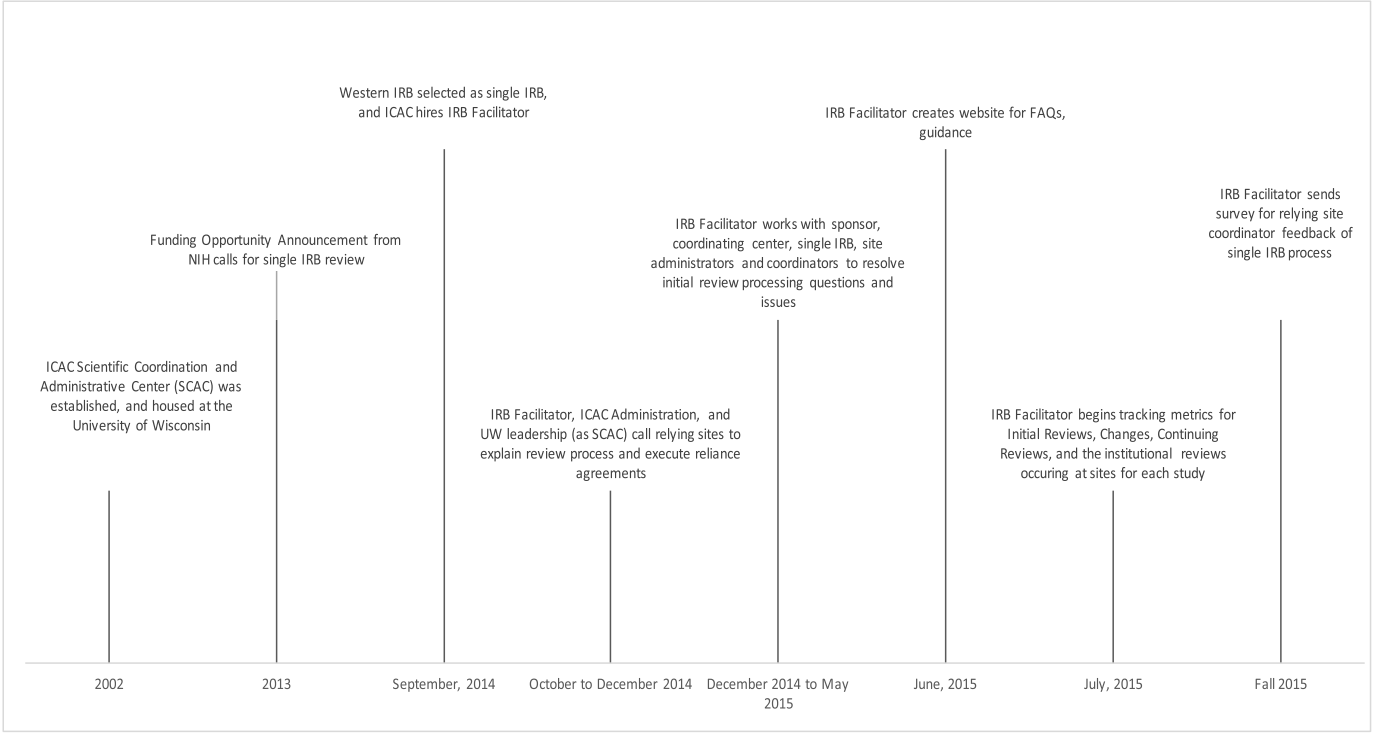


Fig. 1. ICAC single IRB process milestones.

b. Checklist of Site Requirements for Consent

The IRB Facilitator asked each site's IRB administrator to complete a checklist of local requirements for consent language in the following areas:

- pregnancy testing in minors,
- compensation for injury,
- communicable diseases reporting,
- data collected about illicit drug use/alcohol abuse,
- genetic testing,
- commercial products,
- specimen banking, and
- "other" section for language required by policy or state law not captured in the other areas.

These areas were identified as the most likely needing locally required language given the subject populations to be enrolled. The checklist noted that core elements of the consent document would be standard across all sites (e.g., risks, benefits, alternatives). The completed checklists for all sites were provided to NIAID to incorporate its template compensation for injury language with each site's institutionally required compensation for injury consent language. The final checklist for each site was provided to its IRB administrator for approval. When complete, the checklists were provided to WIRB for review by its Executive Policy Committee (EPC). After approval by the EPC, WIRB then established its own processes for including the requisite language for each site's consent documents during IRB review of each site.

3. What reportable events do you want reported to your site IRB administrators?

As written, the ICAC3 reliance agreement – like many others – requires that events be reported only to the IRB of record in accordance with its policies and procedures. Although federal regulations and guidelines allow institutions to cede review of reportable events to an unaffiliated IRB, they also maintain that these same institutions remain responsible for Federal Wide Assurance (FWA) compliance [3]. This inherent tension results in some differences of opinion as to what type of oversight, if any, local IRBs need to provide for reportable events for studies for which IRB review has been ceded elsewhere. At minimum, many sites want to be informed of any events determined by the IRB of record to be serious. The reliance agreement with WIRB included notification of the Principal Investigator, IRB Facilitator, and the "applicable Consortium Study Site" of any event determined by WIRB to be either serious or continuing noncompliance. Since the ICAC3 reliance agreement did not specifically address *how* local IRBs would be informed of such events, the IRB Facilitator ensured that the ICAC standard operating procedures outlined this process. Sites varied on what events should be reported to the local IRB (see Table 1). As a result, the ICAC3 procedure outlines site IRB notification of *any* reports of noncompliance and unanticipated problems occurring at or involving those sites [4].

4. Will your site cede review of HIPAA requirements to WIRB?

All ten clinical sites agreed to cede review of HIPAA requirements to WIRB, which made it possible for ICAC/NIAID to develop a combined consent and authorization template. The template HIPAA language was then distributed to all sites' IRB and HIPAA administrators to approve before implementation at WIRB as ICAC template language.

5. How will your site manage conflict of interest review for these ceded studies?

Table 1
Local IRB required documentation for ongoing research approved by single IRB.

Site	Ongoing Research				
	Requires submission of ALL amendments for institutional review	Requires submission of changes that affect consents and key personnel	Requires Continuing Review Reports	Requires Study Closure Report	Requires Reportable Event Reports
BA	No	Yes	Yes	Yes	Yes, if meet local reporting requirements
BO	No	Only key personnel	No	Yes	No
CH	Yes	–	Yes	Yes	Yes, if meet local reporting requirements
CI	No	Only key personnel	Yes	Yes	Yes, if meet local reporting requirements
DA	No	Yes	Yes	Yes	Only serious determinations
DE	No	Only key personnel	Yes	Yes	Only serious determinations
DT	No	Only key personnel	Yes	Yes	Only serious determinations
NY	No	Key personnel, flyers to be posted in Milstein, or affecting institutional considerations (e.g., radiation exposure, genetic testing)	Yes (with summary of changes made in the last approval period)	Yes	Yes, if event occurred at site
SL	No	Only key personnel	No	Yes	Yes, if meet local reporting requirements
WA	No	Only key personnel	No	Yes	No

All ten sites had a mechanism in place, or implemented one swiftly, for documenting that conflicts of interest were reviewed prior to ceding review of studies.

6. Does your site have an institutional policy for age of assent?

The IRB Facilitator emphasized the distinction between guidance and policy on this topic. IRBs commonly have guidance about what age assent should be obtained, whether oral or written. As the IRB of record, however, the formal determination about when and what type of assent should be obtained would be up to Western IRB, unless a hospital or institutional policy existed that had to be honored. One site did have a policy on age of assent. To ensure consistency across all sites, ICAC requested WIRB apply this site's assent ages to all sites. Eventually, to further ensure consistency, the IRB Facilitator worked with the data coordinating center and NIAID program managers to submit consent templates for each study that had consent and assent instructions consistent with the one site's policy.

7. Does your site have a policy regarding who can provide consent as a legally authorized representative?

Distinguishing between a guardian of a minor and a legally authorized representative was challenging and ultimately this question was unnecessary for the ICAC3 study population. Any specific questions arising at sites as to whether someone was a legal guardian of a minor would need to be addressed by local legal counsel.

8. Does your site have policies for participant recruitment materials?

Although most sites initially said no, some later realized this was problematic. For example, one hospital would not accept the single IRB's stamp of approval and required some language from the local IRB to be placed on the footer of flyers. This site language, in turn, then had to be reviewed by WIRB. This issue was resolved by including a standard line from the site IRB in the “Other” section of its consent checklist, or by submitting the flyers as “site specific” recruitment material with that site's application to WIRB.

9. How do you want access to approved ICAC study documents?

The IRB Facilitator acknowledged that most sites needed access to site approved documents for post-approval monitoring purposes, or audits, and metrics. The IRB Facilitator offered site IRB administrators access to Connexus, but most sites preferred the study team be responsible for the local site submission and to provide the WIRB-approved site documents within each site's electronic IRB review system, or upon request during audits.

3. Implementation issues (timeline reference December 2014 through May 2015)

The first ICAC3 protocol submitted to WIRB illuminated several issues. Although IRB review of the protocol went smoothly, the site application reviews proved more difficult. Some of the issues identified included obtaining site ancillary reviews, separating IRB review from institutional review in site electronic systems, regulatory concerns raised by the NIH contractor for managing regulatory documents, and site requirements of continued documentation for ongoing research (see Table 1).

A case in point was the model consent approved with the protocol review, which included bracketed areas where site-specific language would be inserted. Problems arose when WIRB tried to determine what specific language was intended to go in some of those brackets. For example, does [site name] mean the institution as a whole or the clinical research unit where research visits were occurring (e.g., Boston University versus Boston Medical Center)? Should the same name be used when the same bracket is listed under the HIPAA Authorization section? Other troublesome areas included [name] and [number] for subjects to use in the questions about the research section as well as the [name of facility] where subjects could receive treatment in the alternatives to participation section. These extremely general brackets left too much room for interpretation, resulting in many administrative errors when site-specific consents were processed.

To improve the process for creating site-specific consent documents, the IRB Facilitator worked closely with Rho and NIAID project managers to identify those areas in the model consent that were causing the most confusion. Some of these areas were eliminated entirely (e.g., [name of facility] in the alternatives to participation section) and others were made more specific (e.g., using [principal investigator's name] instead of simply [name]). Additionally, the IRB Facilitator worked with the WIRB account manager to determine what site application responses could be used for the consent document to ensure the information was accurate (e.g., [site name] was a response provided in each site's application).

After site reviews were approved at WIRB, a number of institutional issues emerged that delayed study activation at some sites. In order to document that institutional requirements (e.g., conflict of interest reporting, completion of human subjects training) were met, several site coordinators were required to complete an entire IRB application because the electronic review systems at their sites were not setup to track institutional requirements for ceded studies. Other institutional issues arose around recruitment. A few sites planned to recruit from hospitals associated with their institutions. As separate entities, these hospitals had their own standards for recruitment, including, as mentioned previously, requiring that the stamp of the local IRB and its approval language be on the recruitment flyer. Another hospital required their name be listed in the compensation for injury language of the consent form if subjects were going to be recruited from their location. That hospital was dropped as a recruitment site.

Around the time when the first sites received institutional and IRB approval, a new challenge arose with the NIAID-contracted entity serving as the manager of ICAC regulatory documents, Pharmaceutical Product Development (PPD). An NIAID project manager was informed by PPD that the reliance agreements signed by the sites were insufficient to confirm the connection of the sites to the master reliance agreement between UW and WIRB, and to connect each protocol to the reliance agreement. The agreements did not list FWA numbers or specific protocols. PPD initially argued that each protocol being ceded to an external IRB from each site should be listed on the reliance agreement in addition to the FWA numbers of the IRBs. PPD further questioned how the authority of the signatory from each site could be confirmed. In support of its position, PPD cited the FDA guidance document from 2006 regarding the use of single IRBs [5]. Lengthy discussion among ICAC administration, IRB Facilitator, NIH, and PPD followed, with ICAC and NIH noting that the 2006 FDA guidance states that institutions can use OHRP's sample IRB Authorization Agreement or develop their own [6]. The IRB Facilitator explained the role of an institutional official [7] as the person from each site who signs the reliance agreements, and that WIRB is not required to have an FWA because they are a private company and do not receive federal funding to conduct research [8]. Further, the IRB registration number for Western IRB is publicly available, including the FWA numbers of the institutions relying on Western IRB in the OHRP Database [9]. Ultimately, after providing the ICAC site subcontracts which further explained all ICAC protocols would be reviewed by a single IRB, PPD agreed that the master reliance agreement with Western IRB and site addendums could be accepted.

The final issue of note concerned IRB documentation requirements for ongoing study activities. Although some ICAC sites were already accustomed to ceding IRB review and what that process looked like through the life of a study, others were new to the process and

uncertain what continued documentation would be needed by their institutions. In turn, the site coordinators became confused and questioned whether they needed to submit a parallel application to their local IRBs for every submission made to the single IRB. Questions also arose about the ability to immediately implement a change approved by WIRB or need to wait for the local IRB's institutional review. For those sites that initially required a local review of every submission to WIRB, the efficiencies of using a single IRB started to be lost. To clarify the review process, the IRB Facilitator created a chart describing what submissions were required at each site for ongoing research.[10] Over the course of ICAC's first eight months, more sites gradually determined that less documentation was needed for ongoing research than they originally expected (e.g., changes in research not involving personnel changes did not have to be submitted locally). HRPP administrators at all sites still required access to the latest approved consent document(s) for post-approval monitoring; administrators were encouraged to contact the IRB Facilitator or WIRB, whenever such access was needed. If requested, HRPP and IRB administrators were also added to the study workspace on WIRB's Connexus™ portal.

4. Results

The IRB Facilitator and ICAC3 leadership collected focused metrics, gathered feedback from stakeholders, and measured cost and savings for the single IRB review process throughout 2014–2016.

4.1. Metrics

Whether a single IRB for multi-site studies is more efficient, while remaining effective in providing a quality review, remains an unproven area. Table 2 shows metrics for three studies under the ICAC2 grant that submitted all reviews to local site IRBs. Table 3, by comparison, shows metrics for the five studies under the ICAC3 grant that have been submitted to a single IRB (Western IRB) (see Table 4).

Funding as a performance site for ICAC required the use of the selected single IRB. The range of time to execution of IRB authorization agreements was from 23 to 76 days, with the average of the ten sites being 46 days.

Some of the greatest efficiencies in using a single IRB were realized in changes of research and continuing reviews. Changes in research were typically study wide. The average IRB review time was 11 days. Continuing review deadlines are synchronized for all sites, and all sites keep the same expiration date. Because the reporting form to the IRB was the same information and format for all sites, the statistical and data coordinating center easily provides all sites with enrollment numbers and relevant information to report.

4.2. Feedback

At one year after the implementation of the single IRB, the IRB Facilitator collected survey results from site coordinators about their overall experience and feedback with the single IRB process. Of twelve responding study coordinators, the overall process satisfaction ranked 3 out of 5 stars, with review time and quality of available guidance ranking slightly higher than three stars. While most coordinators indicated a decrease in regulatory workload, a few indicated no change, or an increase in workload. The most common complaint was communication from the consortium to site coordinators about what changes were submitted to the single IRB for review of an approved protocol. With the regulatory process more centralized, site coordinators felt uninformed about what changes were to occur with each study at their site.

The site coordinators were also asked to provide feedback about their local IRBs' interface with the single IRB process. Most coordinators gave high marks for local IRB responsiveness. Areas of potential improvement for local IRBs included providing a clear submission process for institutional review of studies being ceded to an external IRB, and review time of these submissions.

4.3. Costs

Costs of using a single IRB vary significantly by study and are challenging to quantify. Confounding issues of determining true cost include calculating the difference from using multiple local IRBs versus a single IRB, quantifying costs of education and start-up of using a new process, and varying fee schedules of IRBs.

For ICAC3, costs distinguishable from the prior “local IRB review model”, included:

- funding an IRB Facilitator,
- a guidance website, and
- paying per-review, per site, fees to an independent IRB

Performance site cost savings:

- less personnel salary paid prior to study start-up time, less personnel time spent on regulatory submissions allowing more time on recruitment and study procedures
- less overall study costs for reduced time to recruitment completion with faster turn-around for protocol change reviews

5. Discussion

Throughout the past two years, we have learned that relying on a single IRB for a multi-site research network requires substantial administrative support, continued analysis of efficiency and effectiveness, and ongoing education and infrastructure support for sites to parse institutional and IRB considerations. Roles and responsibilities among the data coordinating center, sponsor, site coordinators, single IRB, institutional administrators, and IRB Facilitator must be clearly defined. What follows are our recommendations to other consortiums considering a single IRB model.

5.1. Recommendations for multi-site consortium investigators

5.1.1. Identify administrative support

Administrative support can originate from the institution awarded the grant, local IRB directors and managers, study coordinators at the data coordinating center and sites, and site clinical trials offices. Identification of available resources will assist the administrative center and investigators to approach a review process that works for the consortium's needs, and to calculate costs associated with implementing a new IRB review process.

5.1.2. Analyze the efficiency and effectiveness of the IRB review process

Empirical data on the use of single IRBs to streamline IRB review in the multicenter setting is scarce. [11] Therefore, it is critical for

Table 2
Metrics of ICAC2 studies.

PROTOCOL	Local IRB Review (days)	Site Start-up (days)[a]
RACR (8 sites)	Ave. 37	Ave. 124 (6 sites with available data)
APIC (7 sites for which data was available)	Ave. 78	Ave. 553 (first 3 sites to start; 4 started later due to finishing another study)
PROSE (6 sites for which data was available)	Ave. 68	Ave. 109

[a] As measured from the date of protocol version 1 to date site received activation letter from Statistical and Clinical Coordinating Center.

Table 3
Metrics of ICAC3 studies.

Protocol	IRB Facilitator Submission to WIRB (days)	WIRB Review (days)	Site Reviews at WIRB (days)	Site Institutional Reviews (days)		Site Start-up (days)[a]
				IRB	Ancillary	
RACR2 (9 sites)	1	22	Ave. 7	Ave. 25.8 (range 3–76)	(0–120)	Ave. 184
URECA 4 (4 sites)	1	24	Ave. 16	Ave. 24 (range 1–51)	(0)	Ave. 93
SCITMO (4 sites)	1	15	Ave. 6	Ave. 15 (range 7–32)	(0–93)	Ave. 213
MUPPITS (9 sites)	1	9	Ave. 7	Ave. 11 (range 3–37)	(0–35)	Ave. 145
CoNAC (4 sites)	1	11	Ave. 12	Ave. 14 (range 3–24)	(0–12)	Ave. 114

[a] As measured from the date of protocol version 1 to date site received activation letter from Statistical and Clinical Coordinating Center.

consortiums beginning to use a single IRB to maintain detailed metrics. Specificity of metrics should include when the protocol was made available to the site coordinators, when the application was submitted to the IRB, how many revisions were requested, and when IRB approval was granted. Additionally, the distinction between IRB review time and other institutional reviews required for site activation should be captured. Other reviews, which are not always incorporated in the IRB review, include Investigational Pharmacy, department approvals, Clinical Research Units, and marketing departments for recruitment material review. Another metric point prior to study-start up is the regulatory document manager (largely, PPD for NIH funded studies) approval. While the IRB review may be faster with the use of a single IRB, the time to study start-up may not be. For accurate cost versus benefit analysis of using a single IRB, capturing this distinction is imperative.

5.1.3. Clarify roles and responsibilities

Roles for the initial review process among ICAC stakeholders were identified in a workflow chart prior to the first study being submitted to Western IRB. These roles continue to be revised as we learn what is most efficient without sacrificing quality. With each change in role or responsibility, there is a discussion and review period with NIH that causes a lag time from identification to implementation. Confusion of roles and responsibilities stems from periods of limbo. At minimum, a general workflow should be established prior to the first study submission to a single IRB.

5.1.4. Account for the budget of education and infrastructure

As NIH moves forward with a policy to require use of a single IRB in multi-site studies, it will be imperative that education and infrastructure support be provided to awardees for the review of institutional requirements and the review flow to single IRBs. Our experience has matched research by the Clinical Trials Transformation Initiative (CTTI), which found "… many perceived barriers relate to conflating responsibilities of the institution with the ethical review responsibilities of the IRB." [12] There is a lack of understanding of how to implement the separation of institutional requirements and IRB review. For example, NIH project managers for ICAC had the following questions regarding the separation of WIRB review and institutional review (conducted by local IRB offices):

1) What documents do the local IRB's review and approve (i.e. consents)?
2) Do all of the site IRB's review the same documents?
3) Is there a local IRB stamp on the documents? If so which ones?
4) Can the local IRB's change any of the language in the documents approved by WIRB?

For ICAC, the IRB Facilitator role has been crucial to assist with questions that arise about institutional concerns, monitor metrics, and provide guidance to researchers and administrators. It was quickly realized that there are many frequently asked questions and reoccurring concerns by sites, the data coordinating center, and the sponsor. The solution for these questions was to create a website to house common questions and responses. Common questions in the beginning included what documents to submit and to whom, how to navigate the single IRB website, and how to address errors in documents approved by the single IRB. Later, more substantive questions arose regarding institutional considerations for coordinators conducting research at other locations that were all approved by the single IRB, and how to address protocol deviations that met the site reporting requirements, or the sponsor reporting requirements, but not the single IRB reporting requirements. Consortiums should have a clear budget outline for support to assist sites with the philosophical, regulatory, technological, and process questions.

5.1.5. Anticipate single IRB unfamiliarity with consortium's portfolio of research

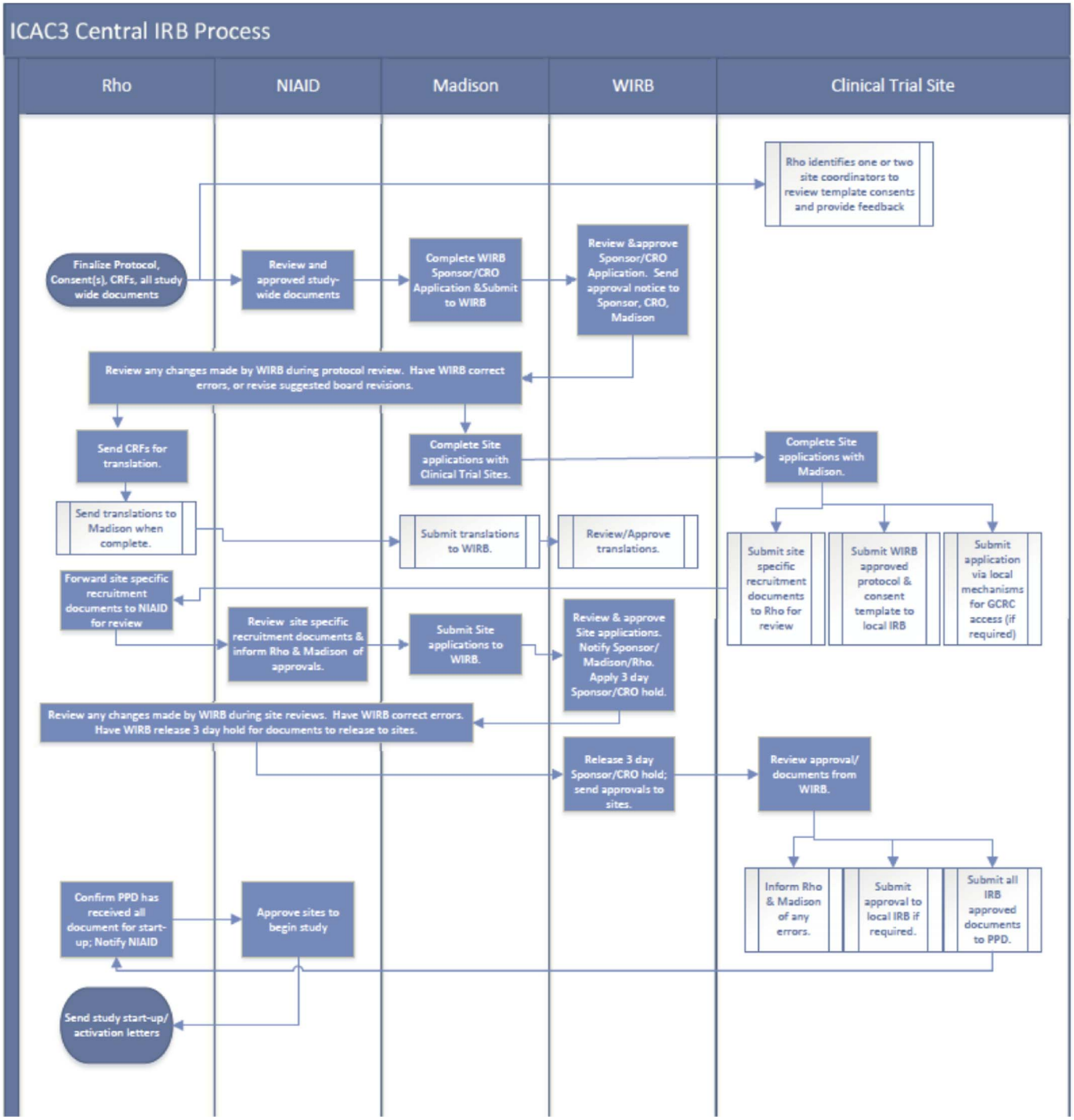
While most site IRBs had historically approved studies with allergy skin testing procedures as minimal risk, Western IRB conservatively determined the procedure greater than minimal risk for the child population of ICAC studies. This led to minor differences in procedure from prior ICAC studies, such as the board requiring two parents' consent, but also a major hurdle for some institutional reviews. One site made an institutional decision not to allow research in children determined by an IRB to be greater than minimal risk with no prospect of direct benefit. Due to the more conservative determinations, the consortium had to change a study protocol to remove a procedure and add benefit to the study in order for all sites to participate. [13] For future submissions to the single IRB, the consortium carefully considered which procedures to include in the study, and elaborated in the protocol on the safety measures in place, experience and training with procedures in the study population at participating sites, and potential benefits.

5.2. Recommendations for NIH to consider

5.2.1. Provide a template reliance agreement

When ICAC drafted a reliance agreement between Western IRB and University of Wisconsin (the administrative center), the agreement was based on the existing agreement the two parties had for industry sponsored research reviews. The amendments to the main agreement were drafted for each site based on the guidance set forth by the Office of Human Research Protections, which states in part that "parties involved may develop their own agreement." [14] After all ten sites had signed the agreement, and the first study was submitted and approved by Western IRB for all sites, the document regulatory manager, PPD, determined the reliance agreements were not sufficient. Issues PPD cited included not having enough information about all of the sites in the main agreement between UW and Western IRB, not having the FWA number of the sites on each site amendment, not having a sufficient link between each consortium study and the agreement, and not having the title of each institutional official clarified on site amendments. PPD cited 2006 guidance from the FDA for the noted concerns. [15] While these concerns were ultimately resolved, it took approximately 3 months, and no site could begin the IRB approved study during that

Table 4
ICAC3 single IRB document flow.



time. If NIH requires the use of a single IRB for multi-site studies, we recommend having a model reliance agreement that will meet the needs of NIH and contractors, or guidance for required components. We recognize here that the recent SMART IRB initiative, funded by the National Center for Advancing Translational Sciences, could resolve the issue of reliance agreements. At the time of submitting this article for publication, 265 institutions have signed on to the SMART IRB reliance agreement, 64 of which are Clinical and Translational Science Award (CTSA) sites. [16].

6. Conclusion

In the third year of using a single IRB, ICAC3 is now focusing on continuing process improvements, with greater emphasis on how site coordinators and investigators navigate institutional reviews when using an external IRB. For other consortium investigators anticipating single IRB requirements, we recommend collecting detailed metrics to provide empirical evidence of any savings, or issues, provided by the single IRB process. This evidence can be shared across institutions, research networks, investigators, and funding agencies to further the

efficiencies in ethical, efficient clinical trial implementation and management.

Acknowledgements

We would like to thank the following people for their valuable contributions:

From University of Wisconsin-Madison:Nichelle Cobb, PhD, Director of Health Sciences IRBs, Lisa Wilson, Senior University Legal Counsel, and Pat Heinritz, retired Administrative Director of Inner City Asthma Consortium.

From Western IRB: Christopher Gennai, Institutions Account Manager, and Randy Czaniecki, Director, Business Development.

From Rho World, Inc: Gina Johnson (formerly with Rho), Stephanie Wellford, Melissa Yaeger, Monica Luthringer, Amanda Smith, Cindy Visness

From National Institute of Health: Katherine Thompson, Steven Sigelman, and Peter Gergen, M.D.

Funded by NIAID/NIH (AI-114271). Supported by grant UL1 TR000427 from the Clinical and Translational Science Award program of the National Center for Advancing Translational Sciences, NIH.

References

[1] Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, NOT-OD-16-094, https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html.

[2] W.W. Busse, The national Institutes of allergy and infectious diseases networks on asthma in inner city children: an approach to improved care, J. Allergy Clin. Immunol. 125 (3) (2010) 529–539.

[3] 45 CFR 46.103(b)(5), and Terms of the Federal Wide Assurance for the Protection of Human Subjects (June 17, 2011) http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html.

[4] http://www.icaccirb.orghttp://www.icaccirb.org(July 2015).

[5] Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials (March 2006). http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127013.pdf.

[6] See ref. 5, (March 2006).

[7] Institutional Official Responsibilities (Secretary's Advisory Committee on Human Research Protections) http://www.hhs.gov/ohrp/sachrp/sachrpresponse091808.html.

[8] IRBs and Assurances, http://www.hhs.gov/ohrp/assurances/.

[9] Office for Human Research Protections (OHRP) Database for Registered IORGs & IRBs, Approved FWAs, and Documents Received in Last 60 Days, http://ohrp.cit.nih.gov/search/fwasearch.aspx?styp=bsc.

[10] See ref 4, FAQs (July 2015).

[11] D.K. Check, et al., Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature, Clin. Trials 10 (no. 4) (August 2013) 560–567 See also Ann-Margaret Ervin, Holly A. Taylor, Curtis L. Meinert, Stephan Ehrhardt, Evid. Gaps Ethical Rev. Multicent. Stud., 6 November 2015, 350(6261), 632-3.

[12] K.E. Flynn, C.L. Hahn, J.M. Kramer, D.K. Check, C.B. Dombeck, S. Bang, et al., Using central IRBs for multicenter clinical trials in the United States, PLoS One 8 (1) (2013) e54999, http://dx.doi.org/10.1371/journal.pone.0054999.

[13] 45C.F.R. § 45.406. Special Protections for Children as Research Subjects, http://www.hhs.gov/ohrp/policy/populations/children.html.

[14] See ref 3 (June 17, 2011).

[15] Using a Centralized IRB Review Process in Multicenter Clinical Trials (March 2006) http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm.

[16] See www.smartirb.org.