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Consortium for Applied Research Ethics Quality

WEBINAR

Why Do Expedited Reviews Take So Long: And What Can We Do To Fix That?

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Why do Expedited Reviews take sooo long? And what can we do to fix that?

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Director, Pitt IRB (2003-2013)

Director, UCSF IRB (2015-2017)

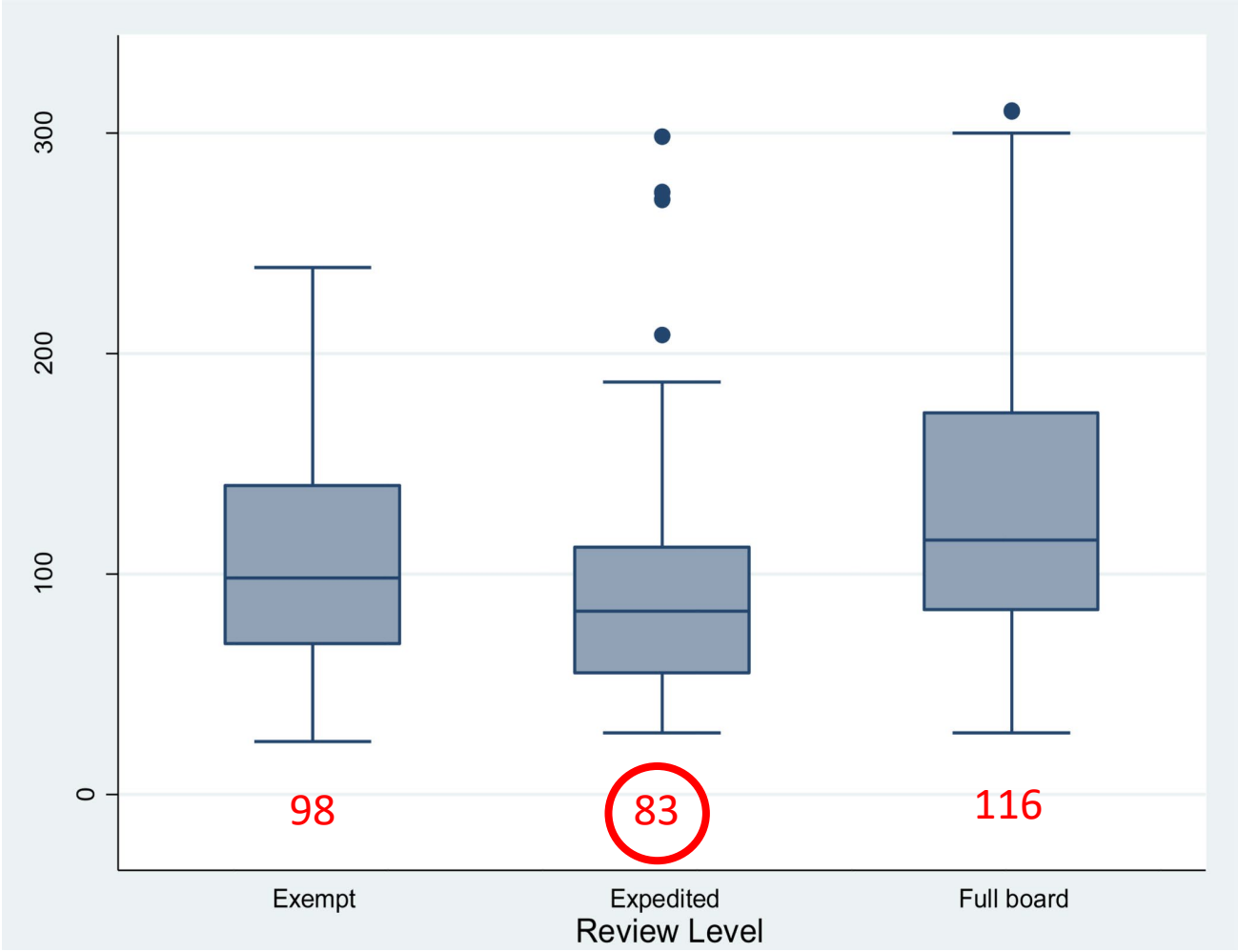
Chair, Novum Independent IRB (1995 – present)

Expedited Reviews: A Gift to IRBs!

Minimal risk research that meets certain criteria can be reviewed by a single IRB member. **45 CFR 46.110**

<u>Implication</u>: Should be significantly faster than Full Committee reviews.

<u>Reality</u>: May be relatively faster, but not always objectively 'quick'!



Time required to review research protocols at 10 VA IRBs
Farley et al., *J Surg Res* 2016; 204:481-489

Variability in Turn-Around Times Across Large University IRBs

Potential Reasons:

Adequacy of staffing / training

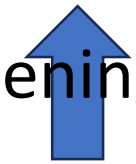
IRB application ‘ease of use’

Quality of web-based resources for investigators

Variations in calculation of turn-around time

	Exempt	**Expedited**	Full Board
A	6	**16**	68
B	5	**19**	38
C	5	**22**	97
D	23	**37**	51
E	14	**48**	60
F	37	**50**	58
G	32	**55**	54
H	9	**57**	85
Average	16	**38**	64

Median calendar days after pre-screening.



Many reasons why reviews take long…

- Assumption that **Expedited** research requires **same** review approach as **Full Board** research
- ‘One size fits all’ IRB application requires too much irrelevant information
- Endless back-and-forth interactions between IRB and researchers
- Willingness to wait FOREVER for responses from investigators
- Failure to properly educate investigators in preparing applications and consent forms

Expedited reviews ***SHOULD BE*** quick!

Approval requires only the following determinations:

- Procedures meet the minimal risk standard [46.102(j)]
- Activities fall into 1 or more of 7 Expedited categories [46.110; 1998 list]
- Consent includes 9 basic elements of informed consent [46.116(b)]
- Optimal privacy and confidentiality protections are present
- Recruitment materials consistent with study/consent and HIPAA
- Institution-specific requirements are met (e.g., training; certification by investigator that responses are accurate)

Challenge: Approve ***80%*** of expedited submissions in 7 days (or less)!

Clock starts after a submission pre-review

- Quick initial review of consent form to get the gist of the study
- Review the study description and consent form
  - Ensure they meet federal requirements for approval
  - Assess internal consistency between description and CF
  - Document with notes and checklists

Implement an *interactive process* to communicate with investigators and get them to make necessary changes to study description / consent forms in *real time*

~ 20% of Submissions may take More Time

These may require additional review / consultation with experts:

- School-based research (permissions from schools; parents)
- Pediatric patients (recruitment; consent/assent; risks may vary by age)
- Inclusion of biospecimens (source; storage; subsequent use)
- Off-site studies – especially non-US (meeting local regulations; staff credentialling; compliance with foreign confidentiality rules; MOUs)
- Non-English-speaking subjects (translations) or those decisionally impaired (determining capacity to consent; managing proxy consent)
- Use of deception


Ongoing Staff Training
Staff Focus on Research Risks and Consent
'Real Time' Video Interactions With Investigator
IRB Office: *Expedited* Webpage
'Suggested' Language Model Consents & IRB Applications
Updated Expedited SOPs
Institutional Systems to Support Data Security, Honest Brokers, etc.
Faster Expedited Reviews
Investigator Compliance Responsibilities

Focus on the Research Risk: It's Minimal!!!

…the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. [46.102(j)]

- For adults, includes virtually any questionnaire or cognitive test; measures of mood / substance use; clinical medical tests (no radiation; no sedation)
  - EEG, MRI, NCV, MEG, & sonograms; blood pressure and other non-invasive medical assessments; finger-stick blood measures; larger blood draws that don't exceed certain volumes and are obtained by an appropriately trained professional
  - Questions about injury to self or others are permissible with an appropriate action plan

Identifying and Documenting Approval Requires a Relatively Modest Amount of Information

Adequacy of application determined from 7 key elements:

1. Study Background and objectives
2. Basic design and funding
3. Participants (age; inclusion criteria)
   - Recruitment methods are appropriate √
4. Methods: **ALL** procedures that will or ***may*** be used are minimal risk √

5. Confidentiality / privacy protections are optimal for study and consistent with University policy √
6. Consent process [separate consent form review √]
   - How done, and by whom
   - Justification for waiver of signed consent, if requested √
   - Potential payments / reimbursements
   - Includes minimal University-required legalistic verbiage, as appropriate √
7. Fits into 1 or more expedited review categories √

Title: Neurocognitive effects of Type 1 diabetes (T1D) in older adults.

Background: Previous research has shown that young and middle-aged adults with type 1 diabetes (T1D) show neurocognitive changes over time (see van Duinkerken et al., for review), but little is known about this in older adults (60+) who are now living longer because of improved diabetes management.

Objective: Determine to what extent T1D affects brain structure, cognition and mood in older adults.

Research Design: Cross-sectional study comparing adults with and without T1D. Funding from the CTSI to cover assessments and participant payments.

Participants and Recruitment: 60 to 80 years old; 15 adults with T1D recruited by co-investigator, Dr. Jones, from his diabetes clinic; 15 adults without T1D who are friends or family members of patients [see attached recruitment scripts].

Methods: Measures include demographics, some or all subtests from the NIH Toolbox cognition and emotion assessment; Beck Depression Inventory; 3 T research MRI without contrast at University Imaging Center; fingerstick blood glucose; blood sample (<2.5 mL) to measure hemoglobin A1c; blood pressure taken by nurse at UIC. Questions about harm to self or others will be reviewed during assessment and appropriate follow-up information provided, if needed. The entire assessment will take about 3 hours.

Privacy/Confidentiality protections: Standard University procedures will be followed to protect research data, but it is possible, albeit rare, that a breach of confidentiality could occur. All assessments are conducted at a university site by personnel trained to protect privacy. Subjects are informed that procedures like MRIs generate information about the participant will be placed in a University Medical Center medical record. This is specified in the consent form.

Consent Process details: The consent form follows the IRB's recommendations / templates. Researcher will discuss the form with participant who will sign it. They will receive $150 for completing the study, or a proportionate amount if they withdraw early. Because this is a research study, using research tasks, no personal results will be provided back, but interested participants can receive a summary of study when it is completed.

Specialized IRB Application Mock-Up

- **Title**: Neurocognitive Effects of Type 1 Diabetes (T1D) in Older Adults.
- **Background:** Previous research has shown that young and middle-aged adults with T1D show neurocognitive changes over time (van Duinkerken et al.), but little is known about this in older adults (60+) who are now living longer because of improved diabetes management.
- **Objective**: Determine to what extent T1D affects brain structure, cognition and mood in older adults.
- **Design**: Cross-sectional study comparing adults with and without T1D. Funding from the CTSI to cover assessments and participant payments.
- **Participants and Recruitment**: 60 to 80 years old; approximately 15 adults with T1D recruited by co-investigator, Dr. Jones, from his diabetes clinic; about the same number of adults without T1D who are friends or family members of patients [see attached recruitment scripts].

- **Methods**: Measures include demographics, some or all subtests from the NIH Toolbox Cognition and Emotion Assessment; Beck Depression Inventory; 3 T research MRI without contrast at University Imaging Center; fingerstick blood glucose; blood sample (<2.5 mL) to measure hemoglobin A1c and blood pressure taken by nurse at UIC. Questions about harm to self or others will be reviewed during assessment and appropriate follow-up information provided, if needed. Entire assessment takes ~ 3 hours.
- **Privacy/Confidentiality protections**: Standard University procedures will be followed to protect research data ("UCx Secure Research Data Repository"), but it is possible that a breach of confidentiality could occur. All assessments are conducted at a university site by personnel trained to protect privacy. Subjects are informed that certain procedures (like MRIs) generate a medical record.

- **Consent Process details**: Consent form follows the IRB's recommended format. Researcher will discuss consent form with participant who will sign it. They will receive $150 for completing the study, or a proportionate amount if they withdraw early. Because this is a research study, using research tasks, no personal results will be provided, but those interested can receive a summary of the study upon completion.

This brief summary of study should provide reviewers with adequate detail to make their expedited determination quickly and efficiently

- Research activities meet the minimal risk standard
- There is a consent process – outlined further in **Consent Form**
  - Risks & benefits are summarized in consent

Optimizing the Consent Form, and Its Review

- Detailed templates ('omit all that doesn't apply') can be very difficult to use, resulting in awkwardly written documents
  - If used, should be specific to minimal risk studies
- My preference: prepare CF as a conversational 'script'
  - Bolding and bullets
  - Figures, tables and pictures
  - Provide ***multiple*** examples on website
- Alternative to Question and Answer format (NCI format)
- Identify staff member who can assist in CF writing

NOTE: "Key Information" summary not needed for briefer CFs

Common Problems with Consent Forms

OASH | Office for Human Research Protections

- Too much information and unnecessary details.
- Overly complex language.
- Dense formatting with minimal white space.
- Written for scientific reviewers.
- Disjointed content copied directly from research protocols or grant applications.
- Complicated legal-sounding language in passive voice.

Suggested (~~Locked~~?) Expedited Research Language

"Use your creativity to develop a format based on your study population"

https://www.hrpo.pitt.edu/building-your-consent-document

Informative but brief suggested statements (but NO legalese) that are developed by IRB and supported by institution, and describe:

- Common research activities (e.g., blood draws; MRI scans; assessment of cognition / mood; etc.) AND associated risks
  - Assistance from experts in health literacy and clinical research
- Sharing of research information and/or specimens
- Protecting privacy and the confidentiality of data
- Use of University-approved systems (and appropriate descriptions)
  - Example: Pitt IRB / Information-Security partnership https://www.hrpo.pitt.edu/electronic-data-security (e.g., Pitt Box)

What is the purpose of the National Children's Study?

The goal of the National Children's Study is to improve the health and well-being of the nation's children. The Study will help researchers understand how the social and physical environment affects children's health, growth, and development. The Study also is interested in how the environment acts together with a person's characteristics, such as genes, to prevent disease and promote health.

Why is the National Children's Study important?

This is the largest and most detailed study in history to examine the health and development of children in the United States. The Study will learn what things in the social and physical environment affect how children develop diseases, both while they are young and when they become adults. Also, there are medical conditions in children that weren't around 30 or 40 years ago or at the levels we see now, including obesity, diabetes, autism, learning disabilities, and cardiovascular disease, to name just a few. The National Children's Study will help us understand why this is happening and what we can do about these conditions and others like infant mortality and injuries.

What kind of study is the National Children's Study?

The National Children's Study is an observational study. Observational studies do not involve asking you to change what you normally do. We will be collecting information about you and, if you are or become pregnant, your child and your child's environment. We will not be asking you or your child to take any medicines or drugs.

How many children will be in the National Children's Study?

The Study will include about 100,000 children from all over the United States. Mothers and fathers also will be asked to participate.

How long will the National Children's Study last?

The National Children's Study will be studying women before and during pregnancy and children from the time they are born until they are 21 years old.

CARS

What you need to know about participation in the Child Affect Regulation Study

CARS

What is the purpose of CARS?

The goal of this research is to use functional magnetic resonance imaging (fMRI) to study how the brain regulates emotion in a sample of young children who are suffering from anger and irritability. This puts them at risk for future mental disorders. This study is the first step toward the longer term goal of using brain imaging to predict which children will go on to suffer from psychiatric disorders (such as anxiety, depression, or bipolar disorder), so that different treatments can be applied at an early age.

What is involved in participating in CARS?

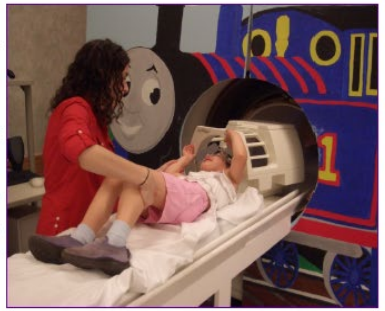
If you decide to join the study, you and your child will first be interviewed by the research team regarding your child's everyday life. During a separate visit, we will complete an MRI scan of your child's brain. If your child is able to complete the scan, we will send him/her home with a picture of his/her brain! Please note that your child may not be asked to participate in the brain scan if s/he no longer qualifies for the study after the interview.

What will happen during the interview?

Both you and your child will be asked questions about your child's emotions, behavior, performance in school, relationships at home and with peers, mental and physical illnesses, and health services used. This interview will be conducted in our offices. You will also fill out some questionnaires about your child's typical emotions and behaviors. This interview is expected to last 2-3 hours.

What will happen during the brain scan?

First, you will be briefly asked by a nurse about any possible metal in your child's body. Then, your child will lie on a table that moves into a large tube containing a strong magnetic field. A cylinder-like head coil will be placed around your child's head to help detect the signals from water and other important chemicals in the brain. During scanning a thumping sound can be heard. Your child will be given ear plugs to minimize the noise. In the scanner, s/he will play computer games and watch movies. The scan time will be under 1 hour. Your child will be able to communicate with the investigators at all times and may be removed from the scanner at any time upon request. Your child should experience no physical discomfort, except those associated with remaining still for the actual scanning period. We will also monitor your child's eye movements, heart rate, or skin conductance during the scan through the use of a small sensor placed on the skin and eye monitoring software.



CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: "Neurocognitive effects of Type 1 diabetes (T1D) in older adults"

Research Project Director:

Biomedical Measures Example

Study Coordinator:

We are conducting research to understand how diabetes affects the brain. We previously found that younger and middle-aged adults with type 1 diabetes show cognitive changes – especially when asked to pay attention and perform cognitive tasks quickly. One goal of this new study, which is supported by funding from the NIH Clinical and Translational Science Institute, is to determine whether these cognitive changes are linked to differences in brain structure. To answer this, we will study about 15 people from Dr. Jones' Diabetes Clinic and also recruit approximately 15 adults without diabetes who are similar in age and background. **{Element 1 – purpose and procedures}**

We are inviting you to consider participating because you responded to our recruitment activities, are between the age of 60 and 80, and do not have any metal (e.g., shrapnel; metal clips) in your body.

As part of this study, you will complete the following procedures. **You will have to make 1 or 2 visits to our clinical center. Total time may be as much as 3 hours.**

- **We will check your blood pressure, draw blood and obtain information from you about yourself, your mood state, and your health**. **We will also administer a series of computer and paper and pencil tests of mental function (e.g., attention, memory, problem-solving) that will take about 45 minutes.** At the beginning of the visit, you will provide a blood sample (less than 1 tablespoon) to measure glycosylated hemoglobin (to estimate blood sugar over a 3 month period) and current glucose levels. Depending on scheduling, you may either go immediately to brain imaging center, or return sometime within the next month for that study. **{Element 1}**

- **MRI techniques will 'take a picture' of your brain**. While the MRI scanner is operating, you may hear a noise similar to someone knocking loudly and rapidly on a metal door. You will be asked to wear ear-plugs to minimize the discomfort of the noise. The scanner is equipped with a microphone and speaker so that you will always be able to talk with the operator or technologist during the study. It is extremely important in these studies that you keep your entire body still and that you especially do not move your head. To help you hold your head steady we may place a strip of tape across your forehead and place extra padding at your ears. Your total time in the scanner will be somewhere between 45 and 55 minutes; the entire session, including set-up time, may take as long as 90 minutes or so. If the MRI Center staff have concerns about possible metal in your body, they will ask you to have an x-ray; you will sign a separate clinical consent form for that, and it will be paid for by this research project. **{Element 1}**

You should be aware that as part of this study, some information that we obtain from you will be placed into Medical Center's medical record systems.

There are a number of possible risks, side effects, and discomforts associated with study participation. **{Element 2 -- risks}**

Unique Expedited Webpage Supports Researchers

- Provide exemplars of approvable **applications** & **linked consent forms** with detailed annotations
  - Surveys / tests / observations with identifiable information
  - Clinical (biomedical) minimal risk data collection (e.g., EEG studies)
  - Experimental manipulations (e.g., strategies to improve memory)
  - Studies of decision making (e.g., business school research)
  - 1 or 2 other frequently encountered study types
- Resources for preparing consent forms and conducting consent interviews should be made available (e.g., training videos)
- Work with Institution to ensure secure data collection and storage systems are available (and their use mandated!)
- If medical records / biospecimens are used, an institution-sanctioned ‘honest broker’ system should be available

How do You Communicate with Investigators? What ***doesn't*** work?

1. IRB reviews application and sends a note requesting clarification
2. Investigator responds when they get around to it
   - Electronic submission systems may make changes especially 'clunky'
3. IRB considers their response inadequate; asks for more or different info
4. Investigator takes time to respond again
5. Perhaps a third round of interactions occurs…
6. After several weeks (and maybe a call), approval may be granted
   - Often, this entire process occurs via notes; calls may be rare

Reality: Poor communication slows reviews at many institutions

‘Real Time’ IRB-Investigator ***Interactions***: The ‘secret sauce’ that can expedite approvals

1. During initial review, IRB staff notes each issue in plain language, states why this is problematic and identifies exactly where these problems are in application / consent form / other materials
   - Can use ‘comments’ on a pdf version of application materials
2. Immediately send this to investigator with request to set up ***a video appointment*** within 3 days and be prepared to discuss and make changes ***in real time – during the call if at all possible***
3. During video call, reviewer sees changes; assured all criteria are met
4. Approval letter can be issued shortly thereafter

One and Done!

For most expedited studies (and most investigators), this is readily do-able

"The Real-Time IRB: a Collaborative Innovation to Decrease IRB Review Time"

Spellecy et al., J Empir Res Hum Res Ethics, 2018 13:432-437

- Rigorous pre-review screening by staff to correct obvious problems
- Following convened meeting review of application, PI and at least 1 other research team member are asked by Committee to clarify issues
- Researchers addresses all deficiencies at a computer in separate room while full committee meeting continues
- After all changes are made in the electronic application, research team returns to meeting and a projector displays the altered application
- Committee then votes to approve (or approve with minor modifications)

Total time reduced 70%: From 63 calendar days to 18.8 days!

Advantages (and challenges) of this approach

- Improves turn-around time dramatically for most applications
- Fosters a more collegial relationship between IRB staff and researchers
  - Staff develop a better understanding of specific research activities and more trust in the integrity of researchers
  - Investigators improve their comprehension of the regulatory landscape and its requirements, and an appreciation for IRB staff
- BUT potentially more effortful for IRB staff
  - Need to go through materials carefully to capture all **relevant** issues the first time, and then prepare clear notes
- AND investigators need to be able to schedule 20-30 minutes and to work on application during the call

Guidance from IRB Staff During Video Conference

Your feedback should include as much detail as possible, including location in document and your ***rationale***

- You are the expert; behave like an educator or mentor and guide the investigator
- Share your best 'plain language' descriptions and help them craft new ones as needed
- Do not 'over-edit' – especially consent forms
  - More (or irrelevant, or legalistic) verbiage increases likelihood that subject stops reading

NOTE: During videoconference, reviewer should take notes and append them to application file to document encounter

Communicating with Investigators: Model Note

"To improve our turn-around times, we have adopted a 'real time' review process. Our staff has examined your application and identified the following issues that need clarification before approval. We ask you to be prepared to ***discuss each point*** with us during a video-conference, and to ***make changes during this conversation***. Our goal is to work collegially to facilitate the review and approval of minimal risk research. By the end of our video call, your application materials – including consent form, SHOULD be ready to be approved. Please set up an appointment (click on calendar) ASAP. If we do not hear from you within 3 days, we will withdraw your application from review."

{Include a listing of issues, **where** they appear in the application, and **why** they need to be addressed}

Reduce the Likelihood of Later Modifications

During your conference, discuss with investigator what types of changes might be anticipated in the future

- Build some flexibility into application and consent form
  - We will recruit approximately 25 people…
  - Cognition measures may include the Wechsler Intelligence Scale, the Wechsler Memory Scale, and the Verbal Fluency test [in IRB application, list ALL likely measures]
  - We may administer several tests of memory, intelligence and problem-solving to measure cognition [consent form should be less specific]

Why is it taking so Long?

- “I don’t want to miss anything important! I don’t want to harm subjects!”
  - Rapid reviews don’t compromise safety when studies are minimal risk
  - So long as your review is thoughtful and your decision-making is documented, all should be OK
  - Do not obsess!
  - Remember: ‘Perfect is the Enemy of the Good’
- Downside of obsessing: Taking too much time harms research endeavor
  - Prevents researchers from initiating their study until IRB approval
  - Delays funding, hiring, and recruitment; slows scientific progress
  - Discourages junior investigators from pursuing research careers
  - Interferes with IRB’s ability to deploy limited resources appropriately (for more complex studies that require additional scrutiny)

“But we NEED to be Ultra-Careful: Investigators aren’t Always Entirely Credible”

- Your intense scrutiny / questioning will not always resolve trust concerns
- You need to accept what has been provided
  - If it is obviously incomplete or wrong, request clarification
  - You may never be able to identify mis-information
- Approval letter should acknowledge this limitation:

  Based on the information you provided to us in your IRB application, this study meets criteria for expedited review [45 CFR 46.110(a); categories 2, 4, and 7] and approval [45 CFR 46.111]. You may now begin this research.

Making these Challenges Work

- Internalize the minimal risk nature of this research
- Reliably initiate ‘real time’ videoconference interactions for all applications
- Develop highly focused webpages for both ‘expedited’ and ‘exempt’ studies, with annotated examples on how to prepare applications, consent forms, and ancillary materials
- Ensure your SOPs clearly summarize how expedited reviews should be processed; qualitatively different from full committee
- Include regular training of IRB staff that include ‘case conferences’
- Change expectation: there should rarely be multiple interactions
- Trust investigators
  - But have them sign ‘Certification of Investigator’s Responsibilities form’

Nothing Ever Changes… Until You Change It