NUTS AND BOLTS OF MULTI-SITE RCTS IN PALLIATIVE CARE

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DISCLOSURE / ACKNOWLEDGEMENTS

No relevant financial conflicts to disclose.

This is not science …. one man's highly opinionated account of a journey with an RCT.

OUTLINE

- Setting up your trial:
  - Choosing your sites
  - Writing your grant
  - Primary and Secondary outcomes
  - Budget
- Good news and bad news: you got the grant
  - Project Management
  - Multi Site IRBs
  - Data collection systems
  - Protocol Manual
  - Opening / training meetings
  - DSMB / DSMP
  - ClinicalTrials.Gov
- Challenges once underway
  - Enrollment, enrollment, enrollment
  - Modifications big and small
  - Rethinking some beginning assumptions

WISDOM TRIAL

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- **W**orking to **I**mprove discu**S**sion about **D**efibrillat**O**r **M**anagement
- 5-year RCT of a clinician-centered patient counseling intervention to improve communication between heart failure clinicians and patients with ICDs
- Randomized by hospital; intervention focused on heart failure clinician; and the patient / caregiver unit of analysis
- Funded by R01 HL102084 - in year 5

WISDOM INTERVENTION

- Small group sessions with heart failure clinicians to improve communication skills
- Automatic reminder system before patient encounters (inpatient and outpatient)
- Aggregated feedback to clinicians about their individual performance

WISDOM TEAM

Sinai

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WISDOM HIDDEN OBJECTIVE

- Encourage clinicians to discuss larger goals of care
  - Not just about management of ICD
  - What patients want given their stage of illness
  - Tailor treatments to those goals, including management of ICDs
- Trying to change clinician behavior
- NOT to have every ICD turned off

SETTING UP YOUR TRIAL

CHOOSING YOUR SITE

- This may seem obvious…but….
  - This is the most important part of your study
  - Its ultimate success depends on this
  - Find a place where:
    - You can get population you need
    - Have on-site colleagues that will advocate for your study
    - Have on-site colleagues with research background

      (not required but it makes your life soooo much easier)
  - **Work on this well in advance!**

WRITING YOUR GRANT

- Don't overpromise
- Think very carefully about your power calculations
  - I don't mean the math. Is the number you want actually achievable?
- Make it clear how you are communicating with sites on an ongoing basis
- Make it easy for the reviewers

D2. Sites (Letters of support from all site investigators and heart failure program directors are included.)

Site	Location	# HF clinic patients	# ICD patients	# of eligible ICD patients/yr
Mount Sinai Medical Center	New York, NY	1500	500	50
University of Colorado – Denver	Denver, CO	800	400	40
Mayo Medical Center	Rochester, MN	1400	570	70
Hospital of the Univ of Pennsylvania	Philadelphia, PA	2000	600	60
Oregon Health and Science University	Portland, OR	350	280	50
Montefiore Medical Center	Bronx, NY	1300	975	50
TOTAL ELIGIBLE PATIENTS PER YEAR 320				

Sites were selected based on interest, administrative support, and absence of a system to address ICD deactivation. At all sites, a core group of 4-8 cardiologists care exclusively for patients with advanced heart failure in both inpatient and outpatient settings. Site investigators will oversee the study protocol and supervise research assistants (RAs). To avoid contamination, no site investigators are heart failure specialists.

MULTI SITE INTERVENTIONS

- Standardization, standardization, standardization
- How are you going to do the same thing at every site?
  - We are rarely drug A vs. drug B, which is easy to standardize
- Important for review, implementation, and generalizability

OUTCOMES: PRIMARY, SECONDARY, EXTRA

- Primary and secondary are your aims
- Extra are what you are going to fall back on if primary and secondary don't work
  - Good for future learners
- However avoid the "it would be interesting if we…."
- Think about temporal trends
  - Where is the field going to be in X years?

NIH $500K ANNUAL CAP

- Assuming you are going for an NIH R01, your cap is $500K
- Turns out that's nothing
  - Especially after a 10-20% cut that you are going to get
- "I never even consider going in for that little."
  - A co-investigator colleague of mine
- Going above the NIH cap means you have to go to NIH to plead your case in advance of submitting your grant
- I regret not doing this

BUDGETING

- How will you motivate the sites?
  - Flat fee per site to fund research coordinator?
  - By enrollment?
- You need a project manager who will do the day to day work of your trial!
  - This person will know more about the trial than you do
  - Not the place to save money in the budget

GOOD NEWS AND BAD NEWS: YOU GOT THE GRANT

MULTIPLE SITE IRBS

- If you think your IRB is bad… or inconsistent….
- Helpful to get your IRB approved first
  - More convincing argument to the other IRBs
  - Some wont even review until the prime site is approved
- 1:1 meetings with chair of your IRB or with other IRBs
  - E.g. one of our sites spent 6 months getting IRB approval which was resolved with a 30 minute Skype call

DATA COLLECTION

- Need a web-based single system
- People SAY they want to enter online in real time…but…
- Build checks into system
  - Our system emails us about every death, hospitalization, and new enrollment. Also emails us when a patient is voided / removed from system.
  - System is color coded so when a patient isn't completed or something isn't completed it is a different color on the research coordinator's screen

PROTOCOL MANUAL

- Need a protocol manual that your research coordinators can follow, that you will update over the course of the study
- Tremendous effort in the beginning, but will last you for X years so put the time in

WISDOM

Working to Improve discuSsions about DefibrillatOr Management

1R01HL102084

Manual of Procedures v1.4

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OPENING TRAINING

- Bring all of your people together for 1-2 days
- Builds team rapport, but also allows you to standardize training
- Have your MOP and Data Collection system set up
  - Hint: build ramp up into your timeline, for us this was month 6 of the grant period
- Think about how you will build in continued training when staff leave, refreshers

DSMB VS DSMP

- Data and Safety Monitoring BOARD vs. Data and Safety Monitoring Plan
- A Board is an outside entity that you can suggest in your application but your institute approves/invites
  - Their role is to monitor safety of subjects
  - Set up separate from advisors/mentors/investigators
  - Can stop the trial for safety (in a good way or a bad way)
- A Plan is an outline of how you will assure safety of subjects at every step of the way
  - The PI can be the head of a dsmP not a dsmB
  - This is for lower risk trials and makes your life easier
  - Consult with your program officer before you submit because this can actually prevent you from getting funded (human subjects concerns DO affect your score)

CLINICAL TRAILS . GOV

- Essential
- Painful at first (sooo many questions……)
  - 12 sections
  - Blank application is 22 pages
- Only do once, update yearly with a single line email stating whether there are changes

PROGRESS REPORTS

- The progress report is straightforward
- You must rebudget and get new subcontracts every year. This will make you want to kill yourself.
  - PLAN AHEAD!!!! THIS WILL TAKE 4-6 WEEKS!
  - The progress report is due 3 months before the year ends.
- Carry over is a wonderful thing. If you have more than 25% you are in trouble.

CHALLENGES ONCE UNDERWAY

ENROLLMENT, ENROLLMENT, ENROLLMENT

- By far the most difficult and ongoing challenge
- Prime site is always going to be more motivated than others

SITE	ENROLLMENT
Sinai	**125**
2	49
3	103
4	99
5	76
6	79

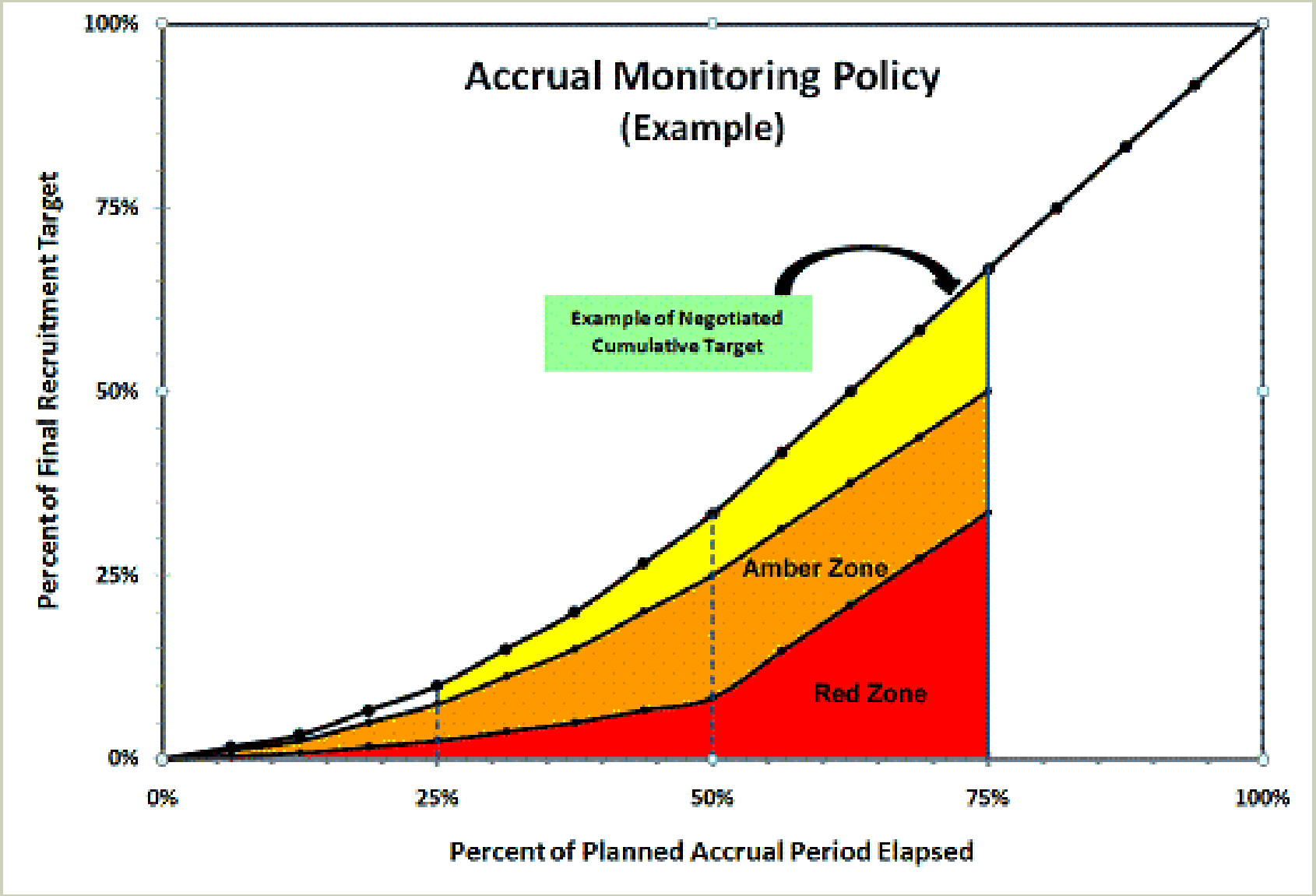
- If NIH they watch this like a hawk – some institute to institute variation

MILESTONE RECRUITMENT PLAN

	2011				2012				2013			
Quarter	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Quarterly Target	0	0	6	18	36	43	43	43	43	43	43	43
Quarterly Enrollment	0	0	1	9	15	29	26	50	41	53	33	32
Cumulative Enrollment	0	0	1	10	25	54	80	130	171	224	257	289

	2014				2015				2016
Quarter	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Jan**
Quarterly Target	43	43	43	43	43	16	46	46	15
Quarterly Enrollment	38	42	39	17	32	28			
Cumulative Enrollment	327	369	408	425	457	485			

- Your Institute will ask for a milestone recruitment plan. They will then track your progress against this chart.
- This chart keeps me up at night.
- No, really, this chart keeps me up at night.



https://www.nhlbi.nih.gov/research/funding/human-subjects/accrual-guidelines#Studies

MODIFICATIONS BIG AND SMALL

- IRB Modifications are the norm
- Adding people, making minor changes in data collection forms, adding questions you forgot
- Remember that a modification has to go through all of your sites – which means you want to batch them to make things easier for the sites

RETHINKING BASIC ASSUMPTIONS

- "This is clinical research in the real world."
  – Henry Sachs, MD

- Once you start you will see that there are some huge things that need to change, but that is the way it works
  - Originally only included people who were NOT VAD and transplant candidates
    - Created a group of patients > 70 who were not generalizable because they weren't considered for advanced therapies
  - Seattle Heart Failure was not performing well and too difficult to find, so broadened entry criteria
  - Originally excluded Spanish speakers

- Is the spirit of the research the same? Are you improving the quality of the finished product?

GOOD LUCK!

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