“Master GC”

Simultaneous Evaluation of Diagnostic Assays for Pharyngeal and Rectal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* Using a Master Protocol

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A Case Study of a Master Protocol

- The Larger Problem
- The study problem
  - The Setup
  - Study Design
  - Regulatory
  - Outcome

The “Larger” Problem

- Big Trials
  - Primary, Secondary, and Exploratory Objectives/Endpoints
    - Trying to maximize the money
    - “Hidden” costs not accounted
- Societal views and understanding of clinical research
  - Volunteerism (10%?)
  - Significant time investment by participant
    - Time to travel to site, even if local
    - In-clinic time; all those assessments!

The “Larger” Problem

- Influence the study design to “answer the question”
  - Get in early
  - Provide options
  - Design protocol-required, site-level processes so the site won’t fail.
- Streamline operations
  - Team must know the specific needs of *this* study
    - Not do what we always do

      Using “template” documents designed for different type of study

      Using the same old text; monitoring (e.g. 100% SDV), safety, “the back third of the protocol” (e.g. consent language)

OK- End of Soap Box Rant

- On to the case study

- **Sarah B. Doernberg, Lauren Komarow, Thuy Tien T. Tran, et al. (Jeffrey D. Klausner),** Simultaneous Evaluation of Diagnostic Assays for Pharyngeal and Rectal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* Using a Master Protocol; **Clinical Infectious Diseases, 2020;71(9):2314–2322**
  - **DOI:10.1093/cid/ciz1105**

Antibiotic Resistance Leadership Group (ARLG)

- The Antibacterial Resistance Leadership Group (ARLG) consists of more than 50 leading experts working together to combat the antibacterial resistance crisis and improve patient care.
- Accomplish this goal through a scientific agenda that prioritizes areas of unmet needs, *innovates clinical trial design*, and informs practice-changing guidelines.
- Created in 2013, ARLG receives its funding from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.
- It is facilitated by the Duke Clinical Research Institute and works under the thought leadership of an executive committee, four component centers, and two principal investigators: Vance Fowler, MD, of Duke University, and Henry “Chip” Chambers, MD, of University of California, San Francisco.
  - One of the Component Centers is the statistics group headed by Scott Evans at GWU.

The Study Problem

- Marketed IVDs (NAATs) for Gonorrhea & Chlamydia
  - Both single bug tests and combo tests
- Labeled for urogenital use only
- Significant off-label use to detect oral and rectal GC infections (i.e. used as LDT)
  - Public health departments
  - Private health clinics
- Do these tests actually work in these other anatomic areas?

The Setup

- Investigator-Initiated clinical trial to answer the question
  - Investigator is the study sponsor – Jeff Klausner of UCLA;
  - ARLG/NIH funded
- Partner with two IVD manufacturers
- Confer with FDA re: Gold Std. for detection of GC
  - NAATs far more sensitive than growth on agar (the gold standard!)
  - Agree to “round-robin” analysis using 3 tests and a tie-breaker (ASIS)
    - Compare each test in turn to the other two.
    - If discordance, the tie-breaker wins

The Setup - Partner with two IVD manufacturers

Table 1. Assay Names, Molecular Methods and Targets, and Laboratory Testing Platforms

Assay	Manufacturer	Target(s)	Laboratory Test Platform
Assay 1	Xpert CT/NG Assay (Cepheid, Sunnyvale, California)	Real-time PCR to detect 2 noncontiguous chromosomal DNA regions from *Neisseria gonorrhoeae* (NG2 and NG4)—both of which must be positive to yield a positive result—and 1 chromosomal DNA target from *Chlamydia trachomatis* (CT1) [20]	GeneXpert System
Assay 2	Aptima Combo 2 Assay (Hologic, Inc, Marlborough, Massachusetts)	Utilizes target capture, TMA, and a dual kinetic assay to detect regions from the 16S rRNA of NG and the 23S rRNA from CT using labeled DNA probes [23]	Panther System
Assay 3	Abbott RealTime CT/GC assay (Abbott Laboratories, Abbott Park, Illinois)	A combination assay that uses real-time PCR to detect a highly conserved region within the *Opa* gene of NG and 2 distinct regions within the CT cryptic plasmid DNA [19]	Abbott m2000 RealTime System
NG tie-breaker	Aptima NG assay (Hologic, Inc)	Utilizes target capture, TMA, and hybridization protection assays to identify the presence of NG 16S rRNA[a] [20]	Tigris DTS System
CT tie-breaker	Aptima CT assay (Hologic, Inc)	Utilize target capture, TMA, and hybridization protection assays to identify the presence of CT 16S rRNA[a] [21]	Tigris DTS System

Abbreviations: CT, *Chlamydia trachomatis*; DTS, direct tube sampling; GC/NG, *Neisseria gonorrhoeae*; PCR, polymerase chain reaction; rRNA, ribosomal RNA; TMA, transcription-mediated amplification.

[a]Both tiebreaker assays utilize distinct molecular genetic targets from the assays under evaluation.

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Anatomic Site Infected Status Composite Reference Method

Comparator NAAT 1 Result	Comparator NAAT 2 Result	Tiebreaker NAAT Result	Anatomic Site Infection status
+	+	Not indicated	Infected
+	-	+	Infected
+	E	+	Infected
+	NR	+	Infected
+	-	-	Not infected
+	-	E	Indeterminate
+	-	NR	Indeterminate
+	E	-	Indeterminate
+	E	E	Indeterminate
+	E	NR	Indeterminate
+	NR	-	Indeterminate
+	NR	E	Indeterminate
+	NR	NR	Indeterminate
-	-	Not indicated	Not infected
-	+	-	Not infected
-	E	-	Not infected
-	NR	-	Not infected

Determined for each anatomic site and organism

Key: NR = no result; E = equivocal result. Initial equivocal results were repeated once.

(partial table)

The Setup

- Partners do lab qualifications
- Third test and tie-breaker test are qualified by sponsor
  - Same testing as our partners
- Rectal matrix for all assay validations

Test Qualification

- LOD & inclusivity,
  - Per FDA guidance on GC/CT
- x-reactivity,
  - The assays have been previously shown not to produce a positive result when tested against an extensive list of organisms, we propose to evaluate only an additional 28 culture isolates commonly found in the oropharynx and rectum.
  - FDA added 7 additional isolates
- interfering substances
  - Toothpaste, mouthwash, bile acids, etc.

Regulatory Design

- Study exempt from §812
- (§812.2(c)(3))
  - A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing:
    - (i) Is noninvasive,
    - (ii) Does not require an invasive sampling procedure that presents significant risk,
    - (iii) Does not by design or intention introduce energy into a subject, and
    - (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Regulatory Design

- Study performed under a waiver of documentation of consent
- 56.109(c) An IRB shall require documentation of informed consent in accordance with §50.27 of this chapter, except as follows:
  - (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or
  - (2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met.
- Participants did not sign anything
- SC marked on source document that consent had been given & initialed

Clinical Study Design

- Enroll 2700 participants at 9 sites throughout US
  - Had to be visiting the clinic for STD testing
- One time visit
  - Data collected anonymously
    - Clinical data collection via patient reported medical history (i.e. Abx use w/in last 14 days)
    - Safety information (if any) collected at the one and only visit
    - No medical record review
    - Randomized collection of 8 swabs from each participant; 4 throat; 4 rectal (yep – that's 21,600 swabs)

      Clinical Swabs First
- Ship swabs to 2 central labs for testing
  - 4 sites to east coast lab; 5 sites to west coast lab
- Statisticians survey results daily to determine which subject IDs would need a tie-breaker
  - All tie-breakers run at one lab

Clinical Study Design – Some Concerns

- Partner companies extremely worried about waiver of documentation & Data collected anonymously
  - Clinical data collection via patient reported medical history
  - Safety information collected at the one and only visit
  - No medical record review (”but how will we do SDV?”)

- Specific written question in Q-Sub meeting package
  - “*The proposed study will enroll subjects in an anonymous manner with follow-on consequences to study operations and monitoring. Does the agency have any comments regarding our proposed plan*?”
  - FDA had to ask their HSP branch; came back as ok as long as IRB’s ok

Clinical study results

- The final study population included 2598 participants out of 2767 enrolled.
- Reasons for exclusion included:
  - a protocol deviation resulting in samples stored outside of the appropriate temperature range (n = 167) at 1 study site
  - withdrawal of consent (n = 1), and
  - Post-enrollment exclusion (n = 1).

- Of the 2598 enrolled eligible participants, there were 2590 (99.7%) with evaluable pharyngeal specimens and 2585 (99.5%) with evaluable rectal specimens.

Clinical study results - Demographics

Table 2. Participant Demographics and Disease Prevalence (N = 2598)

Demographics	No. (%)
Sex at birth	
Male	2059 (79)
Female	539 (21)
Gender	
Man	2010 (77)
Woman	532 (20)
Transgender man	3 (0.1)
Transgender woman	42 (2)
Genderqueer	8 (0.3)
Declined to answer	3 (0.1)
Age, y, median (IQR)	30 (25–41)
Race	
White	1285 (49)
Black	935 (36)
Asian	84 (3)
Other race	145 (6)
>1 race	71 (3)
Unknown/declined to answer	78 (3)
Ethnicity	
Hispanic or Latino	772 (30)
Not Hispanic or Latino	1814 (70)
Unknown/declined to answer	12 (0.5)

Clinical study results - Demographics

Site of enrollment	
A	399 (15)
B	367 (14)
C	367 (14)
D	356 (14)
E	337 (13)
F	290 (11)
G	227 (9)
H	143 (6)
I	112 (4)
Any pharyngeal symptoms	307 (12)
Any rectal symptoms	198 (8)

Clinical study results

Table 3. Performance of Assays Under Consideration for Detection of Pharyngeal and Rectal *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

Site and Infection	PPA (95% CI)	NPA (95% CI)	PPV[a] (95% CI)	NPV[a] (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Pharynx, NG						
Assay 1	94.7 (90.7–97.0)	98.8 (98.2–99.1)	87.1 (82.0–90.8)	99.5 (99.2–99.7)	77 (54–111)	0.05 (.03–.10)
Assay 2	95.1 (91.3–97.3)	98.8 (98.3–99.2)	88.2 (83.3–91.8)	99.6 (99.2–99.8)	78 (54–112)	0.05 (.03–.09)
Assay 3	84.8 (79.4–89.0)	99.5 (99.2–99.7)	94.2 (89.9–96.7)	98.7 (98.1–99.0)	183 (101–330)	0.15 (.11–.21)
Rectum, NG						
Assay 1	91.2 (86.5–94.4)	99.6 (99.3–99.8)	95.4 (91.5–97.6)	99.3 (98.8–99.5)	238 (124–457)	0.08 (.05–.15)
Assay 2	96.5 (92.9–98.3)	99.2 (98.8–99.5)	92.8 (88.4–95.6)	99.8 (99.5–99.9)	127 (80–202)	0.04 (.02–.07)
Assay 3	88.3 (83.2–92.0)	99.6 (99.2–99.8)	94.8 (90.6–97.1)	99.0 (98.5–99.3)	205 (110–381)	0.12 (.08–.17)
Pharynx, CT						
Assay 1	95.9 (86.3–98.9)	99.7 (99.4–99.8)	85.5 (73.8–92.4)	99.9 (99.7–100.0)	303 (151–606)	0.04 (.01–.16)
Assay 2	88.2 (76.6–94.5)	99.7 (99.4–99.8)	84.9 (72.9–92.1)	99.8 (99.5–99.9)	279 (139–562)	0.12 (.06–.25)
Assay 3	84.0 (71.5–91.7)	99.8 (99.5–99.9)	89.4 (77.4–95.4)	99.7 (99.4–99.8)	354 (158–794)	0.16 (.08–.30)
Rectum, CT						
Assay 1	86.0 (80.9–89.9)	99.3 (98.9–99.6)	92.5 (88.1–95.3)	98.6 (98.1–99.0)	124 (76–203)	0.14 (.10–.19)
Assay 2	88.7 (83.9–92.3)	98.7 (98.2–99.1)	88.7 (83.9–92.3)	99.1 (98.7–99.4)	70 (49–100)	0.11 (.08–.17)
Assay 3	83.0 (77.5–87.2)	99.1 (98.6–99.4)	90.0 (85.3–93.4)	98.3 (97.7–98.8)	91 (59–140)	0.17 (.13–.23)

Abbreviations: CI, confidence interval; CT, *Chlamydia trachomatis*; LR, likelihood ratio; NG, *Neisseria gonorrhoeae*; NPA, negative percent agreement; NPV, negative predictive value; PPA, positive percent agreement; PPV, positive predictive value.

[a]PPVs and NPVs were calculated based on the positivity observed in this study.

Clinical study results

- Multiple slides here from the paper

Regulatory End Game

- All data collected by sponsor put in a Device Master File (MAF)
  - Clinical database
  - "raw" data from the platforms
    - Test output is "positive, negative, fail" etc. These words are based on underlying algorithms which, in turn, are based on the chemistry of the test (e.g. PCR with florescence output).
    - FDA wanted the chemistry output results – the raw data
  - 3rd test validation database and raw data
  - Tie-breaker validation database and raw data
- Sponsor provided blinded clinical database, analysis results, and letter of cross-reference to partners
- Partners submitted their 510(k) applications in tandem (FDA knew it was same clinical data)

Outcome

- FDA cleared partner 510(k)s in 65 days
  - From time of last MAF submission to public announcement
    - Initial MAF submission (partial); February
    - Second MAF submission (complete); March

Summary

- Clinical trials do not have to be complex
- Consent has two parts – process and documentation
- Third parties can act as “honest brokers” to perform work that involve multiple parties that may not normally work together

Questions?

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