

Message

From: Samartha Anekal [/O=THERANOS ORGANIZATION/OU=FIRST ADMINISTRATIVE GROUP/CN=RECIPIENTS/CN=SANEKAL]
Sent: 10/31/2013 2:52:39 AM
To: Sunny Balwani [sbalwani@theranos.com]; Daniel Young [dyoung@theranos.com]
CC: Elizabeth Holmes [eholmes@theranos.com]
Subject: RE: hCG precision

I am getting the data from Karthik and will look at it.

From: Sunny Balwani
Sent: Wednesday, October 30, 2013 7:19 PM
To: Daniel Young; Samartha Anekal
Cc: Elizabeth Holmes
Subject: FW: hCG precision

We have run this precision twice now. can you look into this to see what's the issue and why are we missing this.

From: Sharada Sivaraman
Sent: Wednesday, October 30, 2013 7:15 PM
To: Sunny Balwani
Subject: FW: hCG precision

Hi Sunny,

Please see email below. The repeat exercise of entire precision was completed on Tues and the data was sent out to Daniel and Karthik. We still do not pass at the third precision level which is 50 mIU/mL because our precision at that level is 23% but we are only allowed TAE of 15%.

Looping you in on the email exchange and Adam's comments,.

Sharada

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From: Adam Rosendorff
Sent: Wednesday, October 30, 2013 11:53 AM
To: Karthik Jayasurya
Cc: Daniel Young; Sharada Sivaraman
Subject: RE: hCG precision

Hi Karthik

It looks like for the Imulite, the pregnancy cutoff is 30 mIU/mL. The 5mIU cutoff was from Quest Diagnostics Nichols Institute, and they reference the ADVIA centaur. What was the predicate for the validation study?. Shown below are the CVs for the Imulite assay for reference. My concern with relaxing the TAE around or near a decision point is making the wrong call for a patient.

It is important to know the error as well as we can around the decision point. If I could look at the data it would give me a better idea of where we stand.

Thanks,

Adam

Precision (mIU/mL)

	Mean ³	<u>Within-Run¹</u>		<u>Total²</u>	
		SD ⁴	CV ⁵	SD	CV
1	6.5	0.43	6.6%	0.48	7.4%
2	103	3.3	3.2%	4.6	4.5%
3	239	7.6	3.2%	11.1	4.6%
4	438	13	3.0%	21	4.8%
5	3,120	79	2.5%	150	4.8%

From: Karthik Jayasurya
Sent: Wednesday, October 30, 2013 11:30 AM
To: Adam Rosendorff
Cc: Daniel Young; Sharada Sivaraman
Subject: RE: hCG precision

Hi Adam,

Is there a way we can relax the TAE criteria at 50mIU/mL. Currently, our precision stands at 23% which is much more than TAE(15%)

karthik

AE (%)

- | | |
|--|-----------------|
| (1) 5mIU/mL (pregnancy cutoff) | +/- 10% (CV 7%) |
| (2) 50 mIU/mL (should be at least this high 1-2 weeks after conception) | +/- 15% |
| (3) 1,000 mIU/mL (failure to reach this level at 3-4 weeks may indicate ectopic pregnancy) | +/- 18% |
| (4) 5, 000 mIU/L (< is good prognosis for germ cell tumors) | +/- 30% |
| (5) 50,000 (> is poor prognosis, 5,00-50,000 is intermediate prognosis) | +/- 30% |

From: Karthik Jayasurya
Sent: Friday, October 18, 2013 5:24 PM
To: Adam Rosendorff; Daniel Young; Sharada Sivaraman
Subject: RE: hCG precision

Thanks Adam.

Sharada, The method comparison is failing for the decision level 50 mIU/mL since the TAE = 15% and precision itself is 21% at 51.7 mIU/mL, so we don't have any budget for bias. You will have to rerun the precision study at level 3 again to improve precision.

Cheers
karthik

From: Adam Rosendorff
Sent: Friday, October 18, 2013 10:36 AM
To: Daniel Young; Karthik Jayasurya; Sharada Sivaraman
Subject: RE: hCG precision

All

Apologies for the delay- please see the analytic goals below.

Thanks,

Adam

From: Daniel Young
Sent: Thursday, October 17, 2013 7:09 PM
To: Adam Rosendorff; Karthik Jayasurya; Sharada Sivaraman
Subject: RE: hCG precision

What are allowable errors at each of these levels?

From: Adam Rosendorff
Sent: Thursday, October 17, 2013 6:25 PM
To: Karthik Jayasurya; Daniel Young; Sharada Sivaraman
Subject: RE: hCG precision

5 mIU/mL is a key decision level because it defines pregnancy- hCG reaches 2,000 one month after conception, and peaks at 100,000 mIU in the 3rd month.

So we should do:

	TAE
(%)	
(1) 5mIU/mL (pregnancy cutoff)	+/- 10% (CV 7%)
(2) 50 mIU/mL (should be at least this high 1-2 weeks after conception) 15%	+/-
(3) 1,000 mIU/mL (failure to reach this level at 3-4 weeks may indicate ectopic pregnancy)	+/- 18%

- (4) 5,000 mIU/L (< is good prognosis for germ cell tumors) +/- 30%
- (5) 50,000 (> is poor prognosis, 5,00-50,000 is intermediate prognosis) +/- 30%

LLOQ should be < 2mIU/mL (Imulite LLOQ=0.4 mIU/mL)

Adam

From: Adam Rosendorff
Sent: Thursday, October 17, 2013 5:49 PM
To: Karthik Jayasurya; Daniel Young; Sharada Sivaraman
Subject: RE: hCG precision

All

Is the intent to have this test as a pregnancy test or tumor marker test?

Thanks,

Adam

From: Karthik Jayasurya
Sent: Thursday, October 17, 2013 5:47 PM
To: Daniel Young; Sharada Sivaraman; Adam Rosendorff
Subject: RE: hCG precision

According to document sent by Adam, decision levels are as follows:

84702	chorionic gonadotropin	<5	1	5
			2	30
			3	50-500
			4	1000-50000
			5	15000-200000
			6	<5000
			7	>100 000

Two outstanding questions:

- How to determine which levels to evaluate based on these ranges?
- What is the total Allowable error budget at these levels?

karthik

From: Daniel Young
Sent: Thursday, October 17, 2013 11:20 AM
To: Sharada Sivaraman; Karthik Jayasurya
Subject: RE: hCG precision

What are the decision levels for this? Also, do we have the total allowable error? This will be needed to confirm if we need to rerun.

From: Sharada Sivaraman
Sent: Wednesday, October 16, 2013 1:45 PM
To: Daniel Young; Karthik Jayasurya
Subject: hCG precision

Hi Daniel and Karthik,

Did you have a chance to go over hCG precision data? Please let me know what you thought. I am concerned about the progressive jump in signal that we saw and wanted to know ahead of time if a repeat exercise is required.

This will mean reallocating team members to this effort and also require more readers in the Normandy lab.

Please let me know ,

Thanks,

Sharada

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