An investigator's experience with FDA oversight

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NSIGHT consortium

- NICHD and NHGRI funded 4 sites to explore genomic sequencing in newborns
  - Some included NICU or diagnosed conditions
  - Others included healthy newborns
  - Diverse study designs, wide-ranging plans for return of results

Brief overview of NC NEXUS

- Explores exome sequencing in newborn screening
  - 200 “known” affected infants and children
  - 200 “unknown” healthy newborns
- Studying parental decision-making about exome sequencing for their child, and whether to learn about non-medically actionable information
  - Carrier status, adult-onset medically actionable conditions, childhood-onset non-medically actionable conditions

FDA involvement in NSIGHT

- NSIGHT principal investigators received queries from the FDA shortly after announcement of the awards

  “We read with great interest of the recent grant that you were awarded by the NICHD for your clinical trial…”

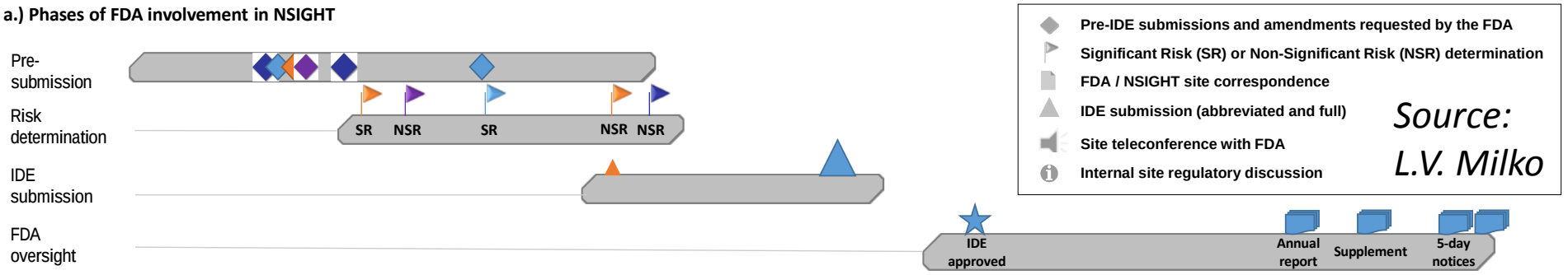
  “(CIDR) … is very interested in the science and clinical development of technologies that can be used for DNA sequencing.”

  “We would like to set up a brief teleconference … to learn more about your study.”

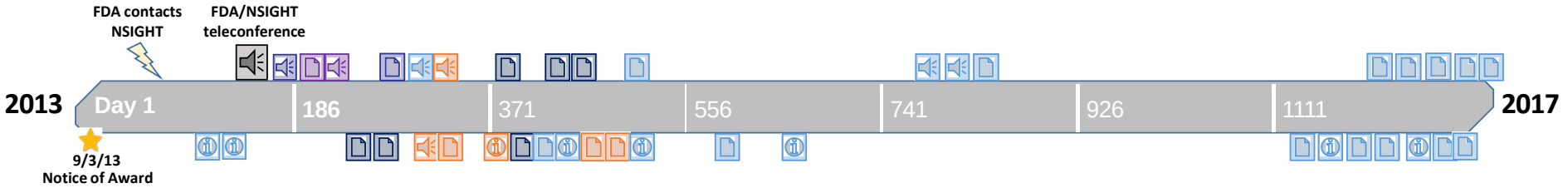
Not the typical order of interaction

- Normally, the IRB oversees human subjects research and determines whether an IDE is necessary
  - Note that the FDA asserts statutory authority to over-rule an IRB determination
- However, all four sites were asked to submit a "presubmission enquiry" to the FDA in order to make that judgment, before any IRB review

a.) Phases of FDA involvement in NSIGHT



b.) Timeline of FDA contact with NSIGHT research sites (colors denote site)



c.) Length of FDA involvement with NSIGHT research sites. Date is the FDA last contact with the site.

Should this even apply to us?

- Research project with no plans to commercialize
- Mostly studying parental preferences and reactions to newborn exome sequencing, not extensively validating a clinical test
- False positives mitigated by Sanger sequencing, false negatives mitigated by usual NBS care

Risk determination

- The FDA determined that the NC NEXUS study posed a significant risk and required an IDE
  - Probably based on sequencing in healthy newborns and return of information beyond childhood onset conditions (ELSI concerns)
  - In particular, our plans to return carrier status and adult onset medically actionable conditions

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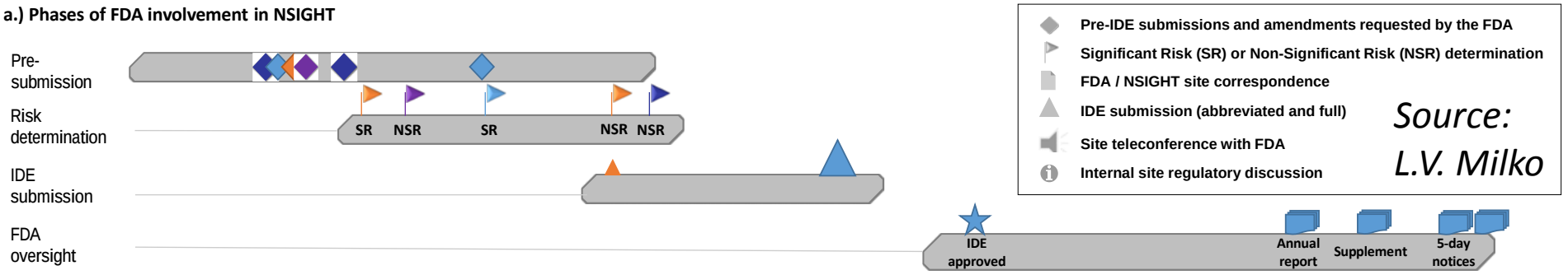

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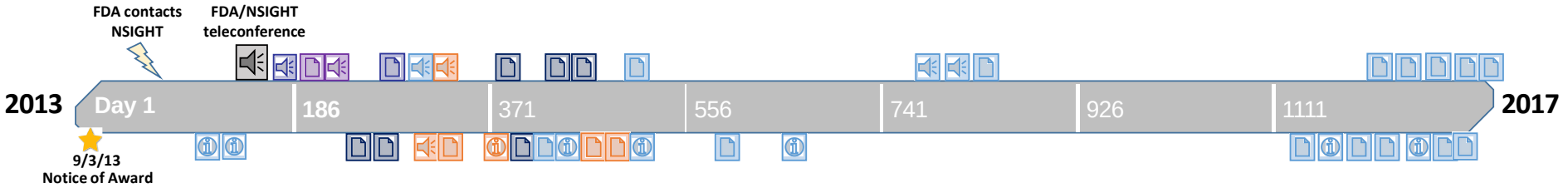

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How does one apply for an IDE?

- Get help!
  - Institutional regulatory assistance
  - Mostly geared toward drug trials, some devices, but no experience with genetic diagnostics
- FDA did not provide any specific guidance or templates to follow
  - We kind of cobbled it together as we went along

What is our device?

- Exome sequencing with Sanger confirmation?
- Electronic decision aid, plus Exome sequencing with Sanger confirmation?
- Electronic decision aid, plus Exome sequencing with Sanger confirmation, plus longitudinal surveys to evaluate parental responses?

Analytic validation is a challenge

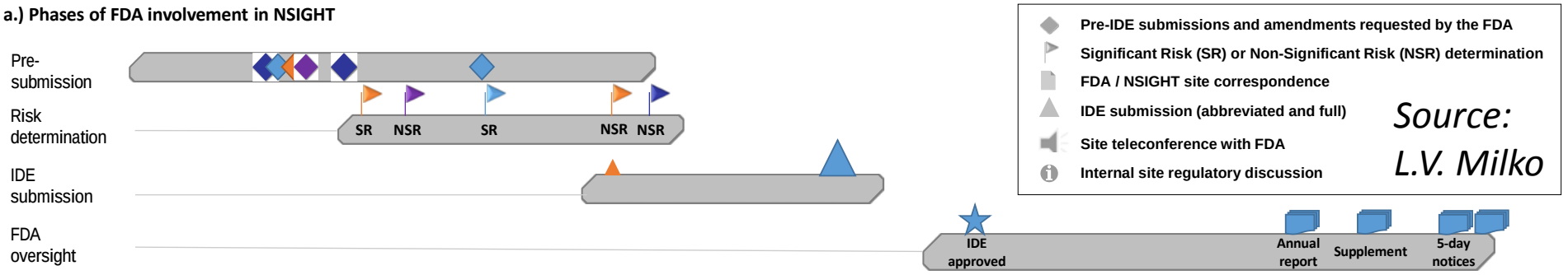
- Commercial saliva collection kits
- Automated DNA extraction in core facility
- Commercial exome library preparation kits
- High-throughput sequencing in core facility
- Standard bioinformatics pipelines
- Molecular analysis and CLIA confirmation

The IDE is about the entire study

- The device itself
- The population in which it is being used
- The return of results policy
- The potential for risk (not likelihood)
- No consideration of possible benefit


Post-it
IDE
NC NEXUS
eSubmitter-eCopy name:
66eae243-f6cc-41e8-148f-ec70a277cbbc
Submission Date:
20 November 2015
CD 1 of 1
Dr. Cynthia M. Powell
University of North Carolina at Chapel Hill
Original IDE Application
IDE Number: Q140207
CD 1 of 1

a.) Phases of FDA involvement in NSIGHT



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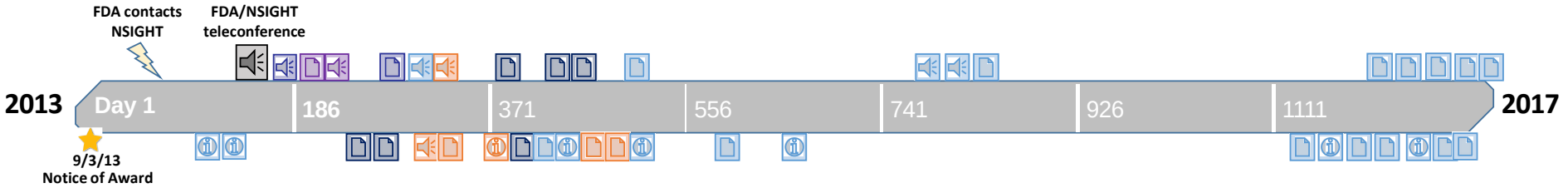

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Conclusions

- FDA oversight is necessary to ensure that products reaching the marketplace are safe and appropriately validated
- However, it adds significant complexity to conducting academic research, beyond what a normal IRB protocol entails
  - Including reporting requirements and processes for making modifications to protocol
- Investigators considering translational research with return of results to participants should discuss risk with their IRBs!

Acknowledgments

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  - Especially Laura Milko

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UNC SCHOOL OF MEDICINE

NCNexus
North Carolina Newborn Exome Sequencing for Universal Screening