Infant
Irish Centre for Fetal and Neonatal Translational Research

Science Foundation Ireland sfi For what's next

Challenges of conducting a Clinical Investigation of a Medical Device in Academia

Taragh Keily

Contents

Background

- ANSeR project and ANSeR Clinical Investigation
- Investigational Medical Device: The ANSeR Software System

Product development (prototype to investigational medical device)

- Intended use & Device Classification
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- Medical Device Directive and meeting the “essential requirements”
- Quality Management System & Risk Management

During the Clinical Investigation - ISO14155

- Device feedback, Device Modifications , Device Defects, Adverse Event reporting
- Investigator’s Brochure and Risk Assessment

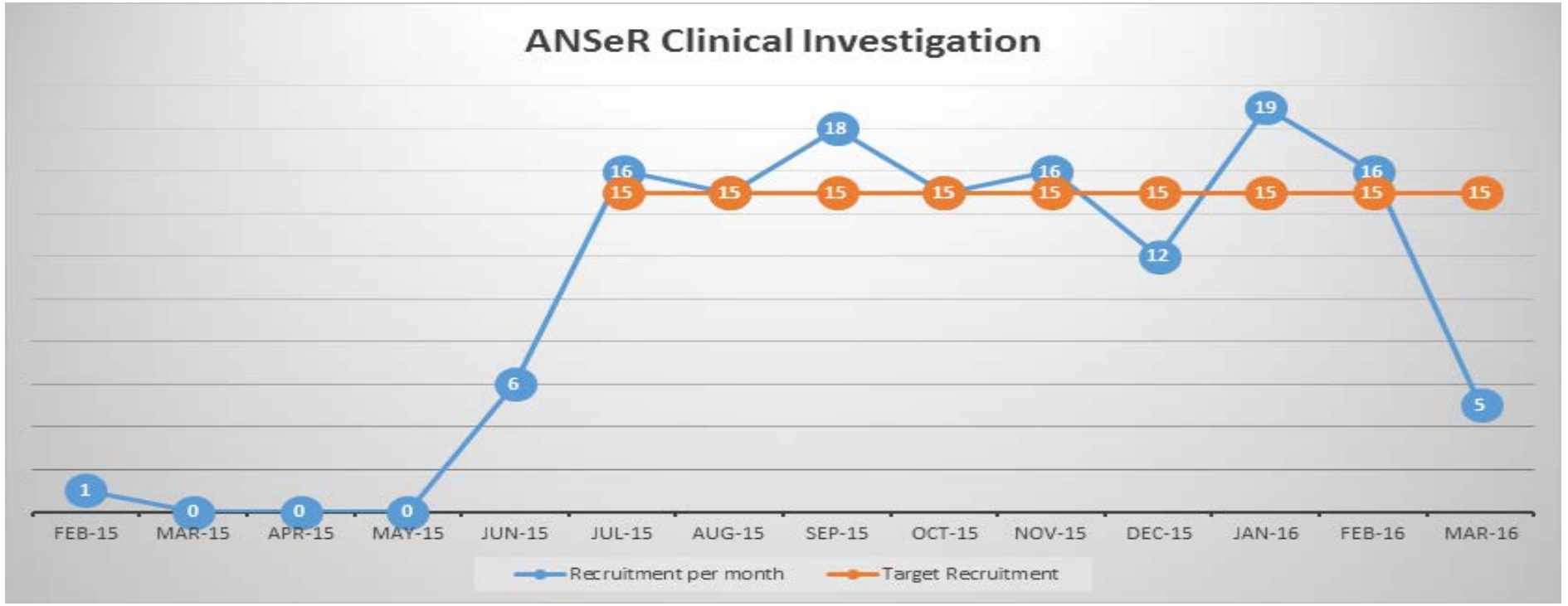
A Multicentre Clinical Evaluation of a Neonatal Seizure Detection Algorithm

- Product development to bring the ANSeR Algorithm to the cot-side ***Complete***
- Strong clinical need for a neonatal Seizure Detection Algorithm
- Phase 1 : Multicentre observational study evaluating usual clinical practice for seizure diagnosis. ***Data analysis ongoing***
- Phase 2 : Clinical Investigation: ***Recruiting***

  "A multi-centre, randomised, controlled, clinical Investigation of a standalone decision support **Algorithm for Neonatal Seizure Recognition"**

ANSeR Clinical Investigation recruitment rate per month
Total Recruitment 139 (N=264) Neonates

- Over 50 % of patient population enrolled (March 2016)



Participating hospital sites

1. Cork University Maternity Hospital
2. University College London Hospital
3. Rotunda Hospital
4. Great Ormond Street Hospital
5. The Royal London
6. Barts Hospital London
7. Karolinska Institute, Sweden
8. Utrecht Medical Centre, Netherlands

EU Competent Authority -Regulatory Approval/Notifications

- Ireland
  - Healthcare Products Regulatory Agency **(HPRA)**
- Sweden
  - Medicinal Products Agency (**MPA**)
- UK
  - Medicines and Healthcare products Regulatory Agency **(MHRA)**
- Netherlands
  - Dutch Health Care Inspectorate **(DHCI)**

ANSeR Core Team at UCC

Prof Liam Marnane, Prof Geraldine Boylan , Dr Janet Rennie, Dr Gordon Lightbody

CUMH	Engineering
Clinical Study Manager Mairead Murray	Software Engineer Denis Dwyer
Investigational Monitor & Clinical QA Jackie O'Leary	Software Validation Consultant
Clinical Project Manager Jean Conway	Project and Quality Manager Taragh Keily
Research Fellow Ludmila Kharoshankaya	
Vicki Livingston -Statistician	

ANSeR product development

- Software Development to bring ANSeR to the cot side.
  - Development of Real Time User Interface
  - Industry Partner: EEG file acquisition
- International standards for ANSeR Development & regulatory compliance.
  - ISO13485: Medical Device Quality Management Systems
  - EC62304:2006 - Medical device software - Software life cycle processes . Commercialization pathway
  - ISO14971 2012: Medical devices - Application of risk management to medical devices

Device Description

- The ANSeR Software (supplied by UCC) is installed on a hospital laptop for the Clinical Investigation
- The hospital laptop is connected to the Nihon Kohden EEG Acquisition System.
- The NK 1200/EEG is used within it's CE marked 'Intended Use'.

ANSeR Software System Device Classification

- Intended use: "*The intended use of the ANSeR Software System is either as a real-time **decision support tool** to assist in the diagnosis of seizures in neonates ≥36 GA, or as a standalone review tool to analyse seizures in a post-hoc environment. The ANSeR Software System is intended to provide a reliable, effective, objective and intuitive means of identifying EEG seizures in the neonate.*"

- Class 2a **Investigational** Medical Device

  under Medical Device Directive 93/42/EC as amended

- 'Standalone software' per MEDDEV 2.1/6.

Is it a Clinical Investigation?

- SUMMARY- Purpose of Clinical Evidence (CER + Clinical Data)
  - Clinical Evidence is required to demonstrate compliance with the MDD Essential Requirements.
  - If the Essential Requirements cannot be met using the existing Clinical Evidence, then a new Clinical Investigation is probably required to fill in the knowledge gaps.
- Clinical Evidence is also required to support adoption of new technologies

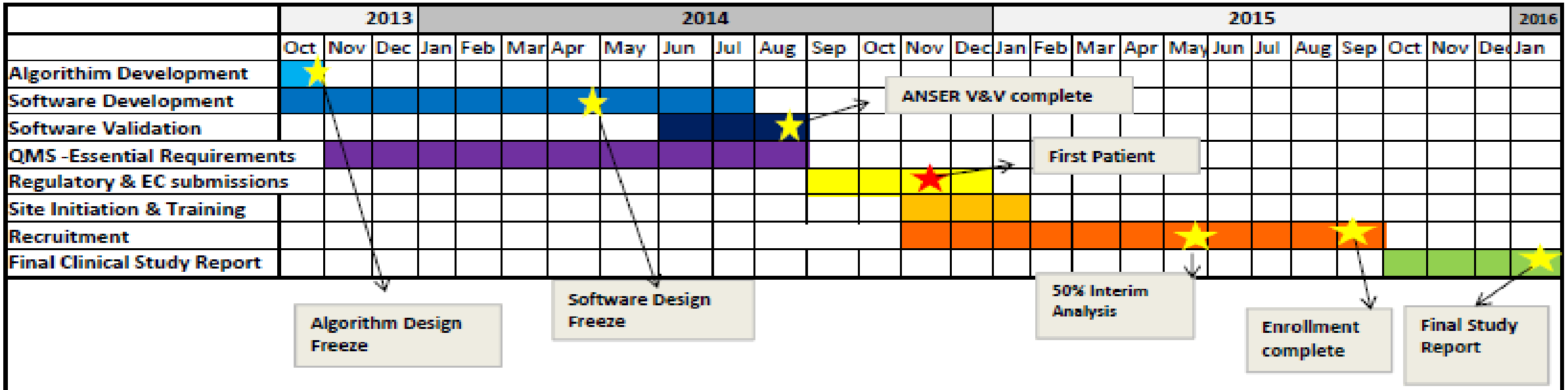
Investigational medical device (ISO14155)

- medical device being assessed for safety or performance in a clinical investigation

NOTE 1 This includes medical devices already on the market, that are being evaluated for new intended uses, new populations, new materials or design changes.

- An investigational Medical device must meet all the applicable essential requirement of the MDD apart from those under investigation.

ANSeR Project Timelines
as at 1st April 2014



RISKS:

1.Any delay in product development activities, including user interface changes, will directly impact the start date of the Clinical Study.

2. The USER INTERFACE design cannot change after design freeze on 30th April 2014 without further delays to study start up.

3. The above timlines are based on Nikon Kohden providing EEG machines to Clinical Study Sites by the end of June 2014, to allow time for training. Any delay or change in relationship between NK and UCC will impact these timelines.

4. Approval (Regulatory , Ethics, Hospital Administration) approval timelines vary between countries due to local requirements. Some sites may get through the approval process in 90 days and others may take up to 180 days.

Table 5: ANSeR Software Development Milestones, Activities and Deliverables

	Responsibility	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd	Tbd
SW Development Procedure	Project Mgr	■	■	■	■	■	■	■	■														
Risk Procedure	Project Mgr				■	■	■	■	■														
1. Software development plan	Project Mgr	■																					
2. Risk Management Plan (RMP)	Project Mgr		■	■	■																		
3. ER Checklist: Annex C 14971 Checklist.	Project Mgr		■	■	■																		
4. Product Requirements	Project Mgr	■	■																				
5. PHA,	Project Mgr		■	■	■																		
Design review of Inputs	Design Review Team					■																	
6. Functional Specification	SW Val Eng				■	■	■																
7. Design Specification	Software Eng					■	■	■															
8a. DFMECA REV1.	Project Mgr						■	■	■														
9. Design Qualification: Protocol	SW Val Eng							■	■														
9. Design Qualification: Report	SW Val Eng								■														
Design Review of Outputs DESIGN FREEZE	Design Review Team								■														
10. Coding DO	Software Eng									■	■	■	■										
11. Code review protocol	SW Val Eng									■	■												
11. Code review	SW Val Eng												■										
11. Code review report	SW Val Eng												■										
12a. unit testing, Integration testing Protocol.	SW Val Eng											■	■	■									
12a. unit testing, Integration testing.	SW Val Eng													■	■								
12a. unit testing, Integration testing Report.	SW Val Eng													■	■								
12b. Installation Qualification (IQ) Protocol	SW Val Eng													■	■								
12b. Installation Qualification (IQ) Report	SW Val Eng																■						
12c. Operating Qualification (OQ) Protocol	SW Val Eng														■	■	■						
12c. Operating Qualification (OQ) Testing	SW Val Eng																■	■					
12c. Operating Qualification (OQ) Report	SW Val Eng																	■					
12d. Performance Qualification Protocol	SW Val Eng																■	■	■				
12d. Performance Qualification	SW Val Eng																		■	■			
12d. Performance Qualification Report	SW Val Eng																			■			
8b. DFMECA Rev2.	Project Mgr																			■			
2. Risk Management Report (RMR)	Project Mgr																					■	
13. ER Checklist	Project Mgr																					■	
14. Requirements Traceability Matrix	SW Val Eng								■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Final Design Review	Design Review Team																					■	

Key: ■ : Project Milestone; ■ : Scheduled Activity

Technical Documentation

Generated to support regulatory submissions demonstrate compliance with international standards

1. Software Development Plan	**9. Design Qualification: Protocol and Report**
2. Risk Management Plan and Report	10. Code Review Protocol and Report
3. Essential Requirements Checklist	11. Unit Testing: Protocol and Report.
4. Product Requirements Specification (PRS)	12 Integration Testing: Protocol and report.
5. Preliminary Hazard Analysis (PHA)	13. Installation Qualification: (IQ) Protocol and Report
6. Functional Requirements Specification (FRS)	14. Operating Qualification: (OQ) Protocol and Report
7. Design Specification (DS)	15. Performance Qualification: (PQ) Protocol and Report.
8. Design Failure Mode Effect & Criticality Analysis (FMECA)	16. Requirements Traceability Matrix (RTM)

During the Clinical Investigation

- User feedback is captured through the eCRF.
- Device deficiencies

"inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling."

- Adverse Event and Serious Adverse Event Reporting
  - Weekly reporting to CAs

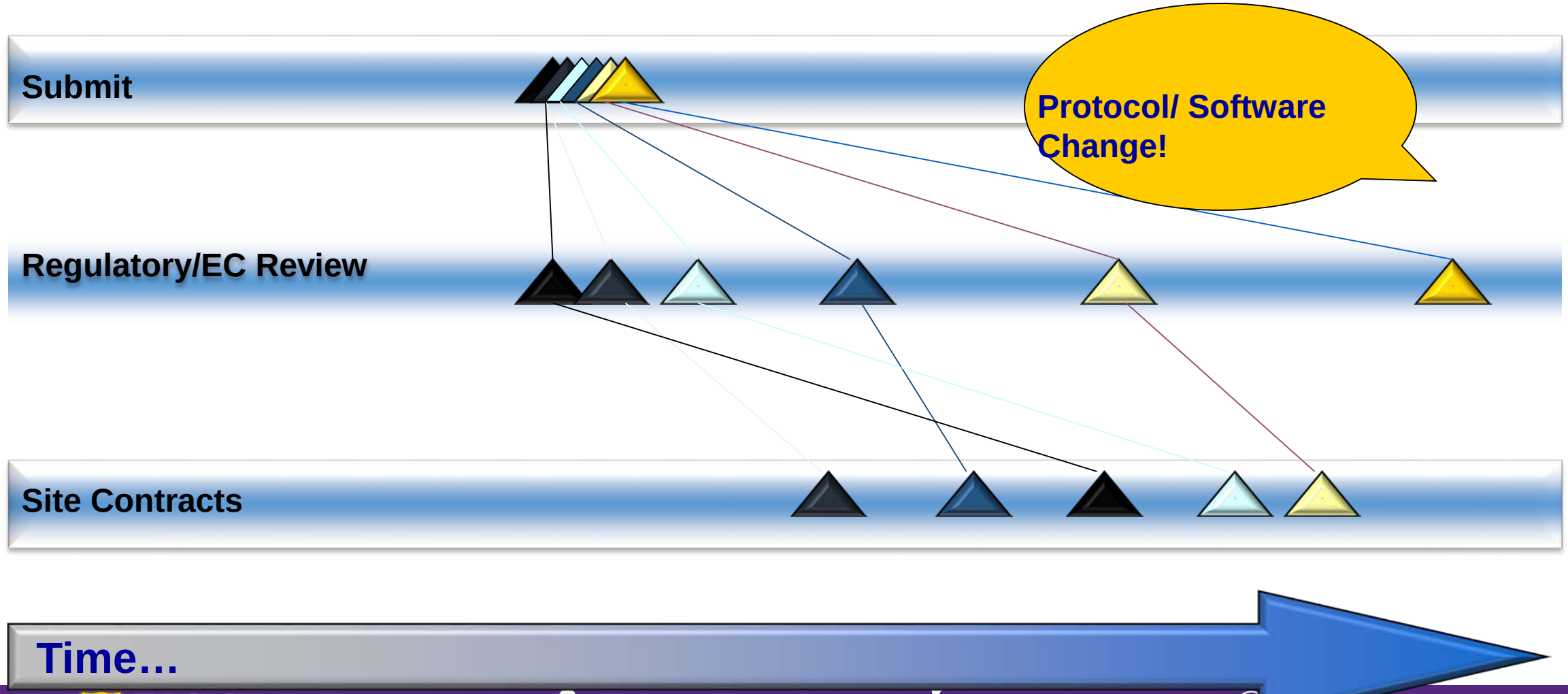
ISO14155 device defects

- **adverse device effect ADE**
  - adverse event related to the use of an investigational medical device

    NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

    NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
- **unanticipated serious adverse device effect USADE**
  - serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report
  - NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Orchestrated Timelines?



Main challenges

- Terminology in standards, regulations aimed at industry manufacturer
- Some “grey areas” for academic studies.
- Understanding of device development process, essential requirements.
- Developing a QMS and execution.

Thank you

Questions