Remote Cardiac Monitoring for Clinical Trials

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Overview

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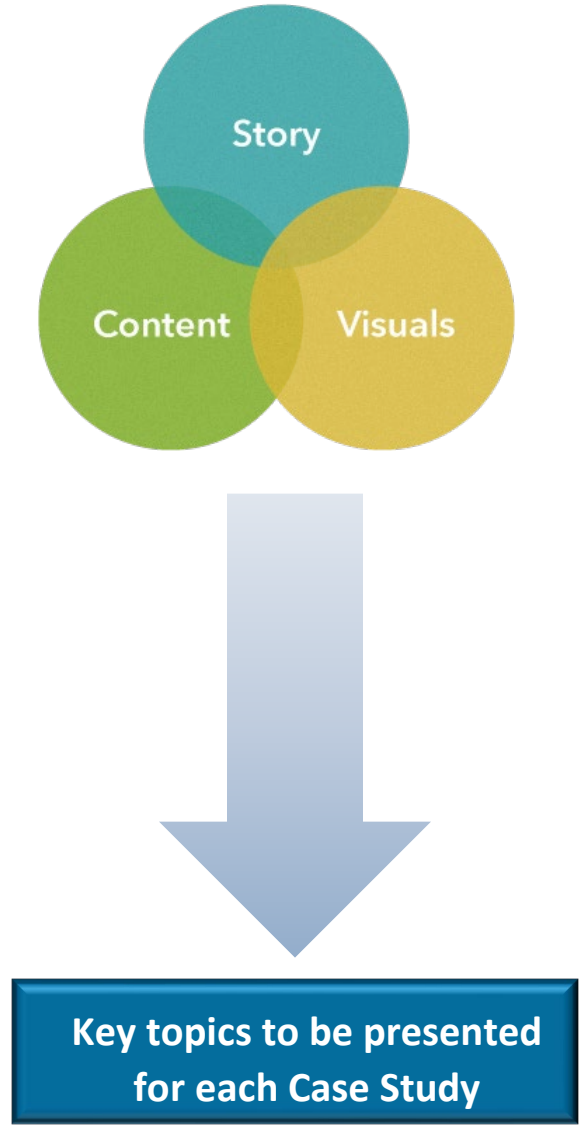
- Q&A panel



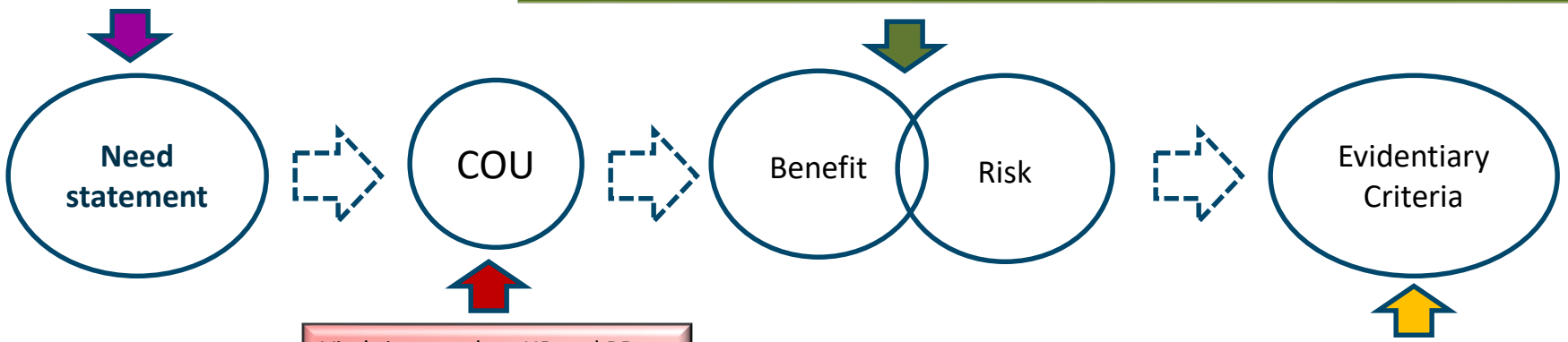
Disclaimer for the Cardiac Monitoring Case Study

- Both studies described in publications used as a starting point for this working group were designed and initiated in Q1 and Q2 of 2016, **prior to** the mobile technologies CTTI recommendations and 2018 Biomarker Qualification Evidentiary Framework FDA Guidance being available publicly

Evidentiary Criteria Framework

- Certain elements of safety profile (HR, RR, body temp) can be built comprehensively in early stage clinical trials using wearable devices to collect dense continuous data both during the clinical pharmacology unit (CPU) confinement and after the discharge from the CPU
- Collect the data in the real-world settings
- Early signal detection can inform dose adjustments or discontinuation of drug candidates with safety liabilities earlier in the drug development process

- **Benefits of continuous monitoring using wearable devices**
  - Earlier detection of a potential safety signal
  - Dose adjustment
  - Early discontinuation of drug candidates with an unfavorable safety profile
  - A reliable pharmacodynamic assessment if related to drug MOA
- **Risks**
  - False negative - missing a potential safety signal
  - False positive - time consuming data review and reporting
  - COU may be different than intended use and indications of use stipulated under 510(k) clearance
  - Missing data
- **Risk mitigation**
  - Validation should be performed according to the COU pertinent to a specific clinical trial
  - Establishing analytical validity and statistical methods for continuous ambulatory monitoring



Vital signs, such as HR and RR, evaluated in normal healthy volunteers for safety monitoring in Phase I clinical trials but may be applied to any stage of drug development

- Biological rationale is well established for conventional safety monitoring
- Device measurement characteristics, reportable range and reference interval need to be established for continuous remote ambulatory monitoring
- Retrospective data analysis and ad hoc if needed
- Confirmation with independent datasets is needed
- Novel data analytics and statistical approaches are needed

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Problem Statement

Clinical trials in normal healthy volunteers (NHV)

The goal of early-stage clinical trials is to establish a pharmacokinetic, pharmacodynamic and safety profile of an investigational drug

- **Early stage clinical trials in multiple therapeutic areas, excluding Oncology, are conducted in NHV**
  - The PK, PD and safety data are collected while study subjects are confined to the clinical pharmacology units (CPU) and after the discharge from the CPU during the follow-up visits
  - The duration of the confinement varies from one to several weeks depending on the study design, investigational compound properties and anticipated/emerging safety profile
- **Safety data collection is done at predefined time points and includes vital signs** (e.g. ECG and laboratory safety tests)
- **The CPU confinement for extended periods of time is inconvenient for study subjects and may not provide the data reflective of normal day-to-day person's activity**
- **Little or no safety information**
  - Other than subject's memory recall, is available after subject's discharge from the CPU and in-between the follow-up visits making difficult to interpret potential safety findings

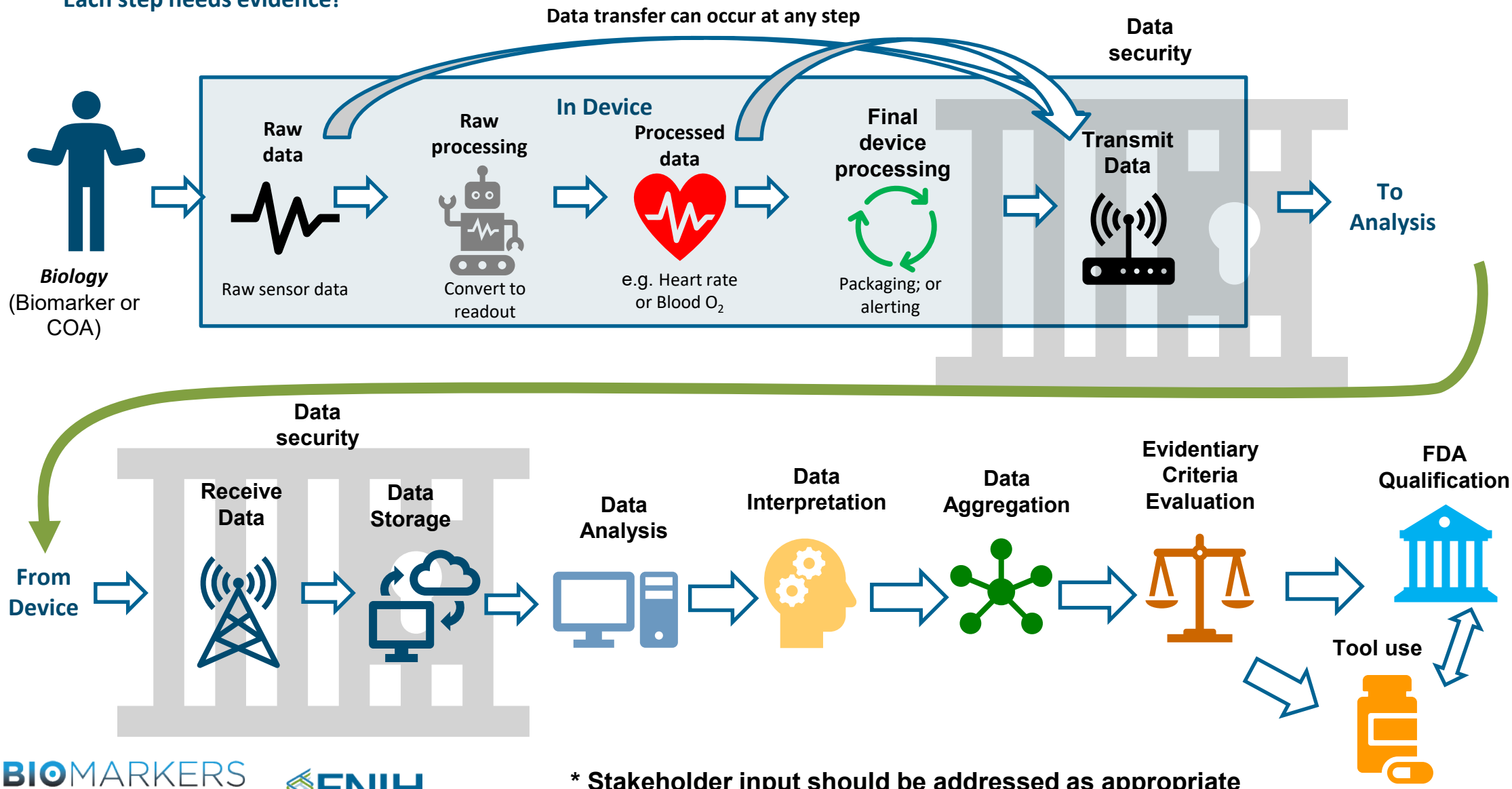
Statement of Need

- **How is this needed in drug development?**
  - Certain elements of safety profile (HR, RR, body temp) can be built comprehensively in early stage clinical trials using wearable devices to collect dense continuous data both during the CPU confinement and after the discharge from the CPU
    - Collect the clinical trial subject data in the real-world setting, a.k.a. “in the wild”
  - Early signal detection can inform dose adjustments or discontinuation of drug candidates with safety liabilities earlier in the drug development process

- **Why take the path of digital measure vs. current modalities?**
  - Data collected at predefined time points – not clear what happens in-between – a signal can be missed
    - Holter continuous monitoring is available for limited duration, e.g. 24-48 h
  - No clear how early safety profile is impacted by activities of daily living, e.g. physical exercise, once the study subjects leave the unit

Flow of data from biology to decision

Each step needs evidence!



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*** Stakeholder input should be addressed as appropriate**

Studies Used for Cardiac Monitoring Case

	Study #1	Study #2
N	6	5
Population	NHV	NHV
1 lead ECG patch-like devices	HealthPatch by Vital Connect • HR, RR, skin temperature • Step count (via an accelerometer)	BodyGuardian by Preventice • HR, RR • Activity counts (via an accelerometer)
Wrist worn actigraphy	Actiwatch Spectrum Pro by Philips (activity counts, physical activity, sleep)	
Duration	10 days confinement period	2 confinement periods separated by at home period
510(k) clearance	Yes	Yes
ECG raw data accessibility	Yes	Yes
Algorithm	Proprietary	Proprietary
In-study data review*	No	Yes*

Study#1 https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12602
Study#2 https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12673

** Not deployed in the study*

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Experimental Design and Key Findings

Study Design

- Exploratory endpoint
- Data "safe harbor“ - not used for any clinical decision-making
- Comparison to conventional safety measures using time matching data points

Operational Execution

- Separate optional informed consent form
- Devices were administered and managed by the site personnel
- The sites were trained to assign a device to a specific study subject and train subjects on device management, e.g. battery recharging

Data Analysis

- All analyses were performed after completing the data collection in all subjects
- Analytical evaluation was carried out by:
  - Comparison to the corresponding conventional measures for HR and RR
  - Conformity of randomly selected HR values (low, medium, high) to the results of ECG tracer manual review
- Face validity of vital sign and actigraphy data was confirmed by examining aggregate diurnal variation patterns

- ✓ Assessment of wearable devices as an exploratory objective in an interventional study is feasible
- ✓ Conventional measurements, e.g. "gold standard", need to be considered carefully
- ✓ Inclusion of appropriate controls is essential

- ✓ Study subjects expect to be compensated for additional study procedures such as wearable devices
- ✓ The sites emphasized the importance of having hands on training prior to deploying devices with the study subjects
- ✓ The satisfaction of study participants with variable devices was high

- ✓ Ambulatory ECG data can be noisy, data review can be time consuming
- ✓ Appropriate data filtering is essential
- ✓ Novel statistical approaches are required to facilitate the review of continuous data compared to the analysis of conventional data collected at predefined time points

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Context of Use (COU)

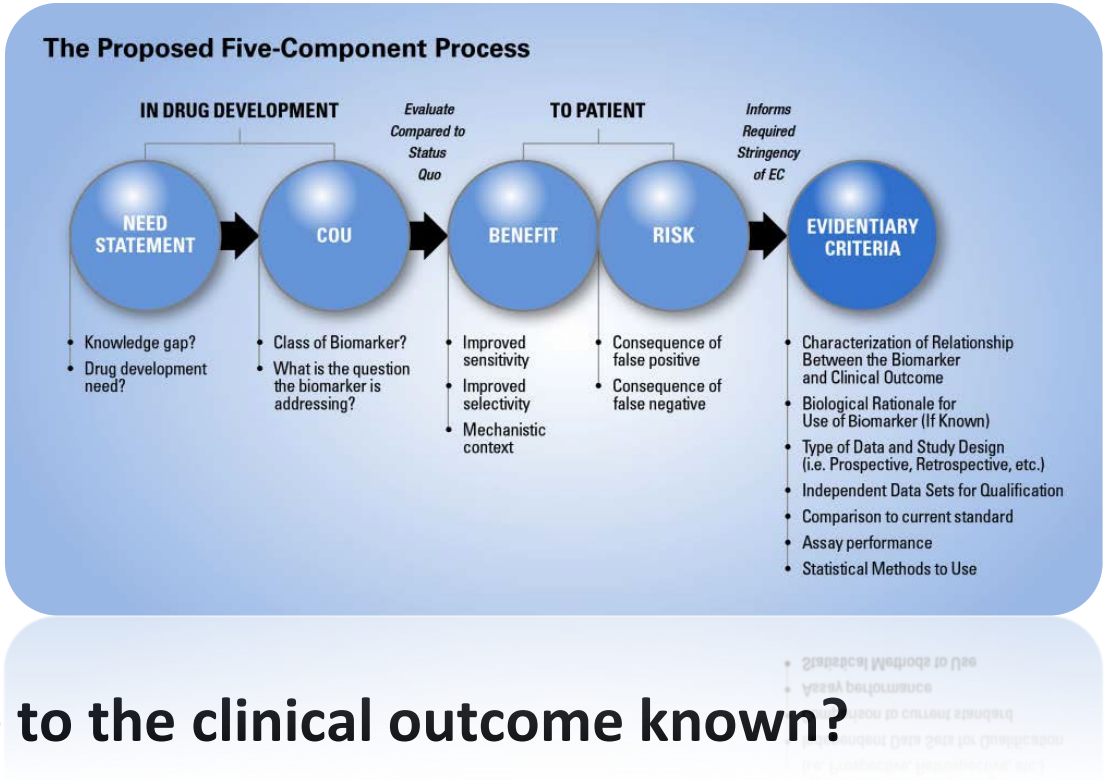
Definition: A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use https://www.ncbi.nlm.nih.gov/books/NBK338448/

- **Does the COU of the device fulfill the need?**
  - **Example 1: Retrospective multimodal analysis of early safety signals is needed**
    - Vital sign (HR and RR) analysis suitable
      - Dense continuous data
      - Physical activity (PA) needed as a part of metadata to interpret the results
    - Cardiac rhythm analysis: more feasible than for real-time, but still requires a lot of manual curation
  - **Example 2: Real-time ad hoc analysis of early safety signals is needed**
    - Vital signs (HR and RR)
    - Rhythm analysis (arrhythmias): analytical validation is key

- **Important considerations:**
  - Analytical validation (what the device is meant to measure) and human factor testing
  - Changes in patient population may require reassessment, e.g. NHV vs. disease population

Relationship to the existing biomarker evidentiary criteria framework

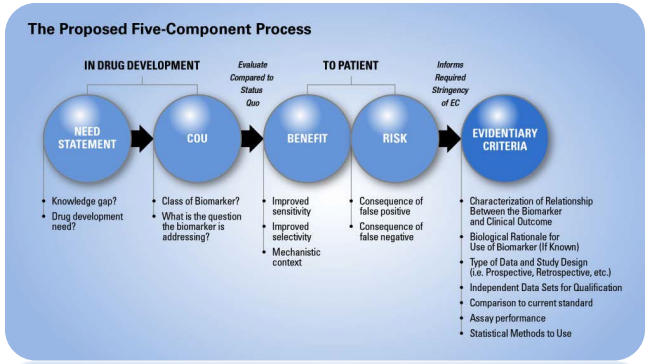
- **Existing Measure**
  - Single-lead ECG for remote monitoring
  - Conventional measurements:
    - 12-lead ECG (resting and supine)
    - Holter monitoring (ambulatory)
    - Manual RR
    - Oral temperature



- **Is the relationship of the remote measure to the clinical outcome known?**
  - Reference ranges – normal/ abnormal are established and apply to both conventional and remote measurements
  - Not all features of the conventional ECG are collected as part of safety monitoring in clinical trials (e.g. QT or PR interval prolongation) are available from a single lead ECG

Alignment with biomarker evidentiary criteria framework

- **What fits?**
  - Variables
    - HR
    - RR



- **What doesn't fit?**
  - Conventional value reference ranges and reference interval
  - Interpretation of continuous data under ambulatory conditions
  - Physical activity by means of actigraphy does not have conventional counterparts for purposes of safety monitoring
  - Skin temperature is highly variable, can be impacted by a number of factors difficult or impossible to control (ambient temperature, clothing, body movements) and difficult to interpret

Study subjects were asked to complete the technology satisfaction questionnaire. The response indicated high acceptance of technology

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Benefit Assessment

- **By qualifying vital sign measurements using single-lead ECG and wrist worn actigraphy devices:**
  - Earlier detection of a potential safety signal
  - Dose adjustment
  - Early discontinuation of drug candidates with unfavorable safety profile
  - A reliable pharmacodynamic assessment if related to drug MOA
- **When in the drug development lifecycle is the measure intended to be used?**
  - Predominantly in Phase I clinical trials, but can be deployed at any stage as needed
- **Is the benefit of the measure to the individual or society?**
  - More effective drug development
  - Easier participation in clinical trials
  - More feedback from the study subjects how they are doing

Risk Assessment

- **Device performance:**
  - What is the potential consequence or harm if the measure's performance is not aligned with expectations based on the COU?
    - False negative - missing a potential safety signal leading to a misuse of certain therapeutics
    - False positive - time consuming data review and reporting
      - Potential signal needs to be verified by a trained professional
  - Data losses due to subjects not wearing devices when unsupervised, connectivity issue etc.
  - Analytical validity – comparison with the raw/ source data to establish accuracy beyond the comparison to conventional measurements
    - Reference ranges and interval are needed for ambulatory conditions

Risk Assessment

- **Regulatory:**
  - COU may be different than intended use and indications of use stipulated under 510(k) clearance
  - Validation should be performed according to the COU pertinent to a specific clinical trial

- **Data analysis:**
  - Correlation and limits of agreement with conventional measurements
    - Limitations: conventional measurements are done at predefined time or continuous monitoring for limited time, e.g. Holter monitoring for 24-48 h – full scale comparison is not feasible
  - Data filtering – what is noise and what is a real signal?
    - Striking the right balance – more analytical work is required using larger data sets

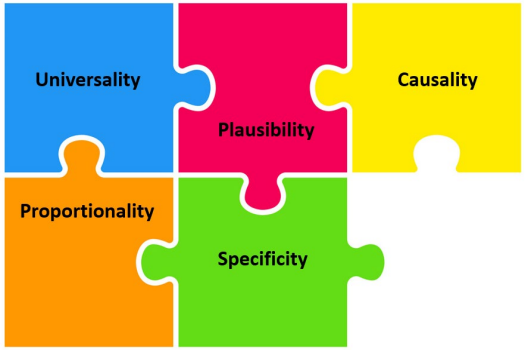
Risk Assessment – mitigation strategy

- **Device performance and regulatory:**
  - Establishing device performance characteristics according to the COU prior to collecting data
    - Access to the raw data is a must – required for both analytical validation and a potential safety signal confirmation during clinical study results review
  - Establishing a minimal threshold of subjects' adherence to contributing the data
    - Prior human factor testing may be required
  - Establishing reference ranges for ambulatory conditions for variables of interest
    - Physical activity data is essential for result interpretation

- **Data analysis:**
  - Establish a process for data review and reporting
  - Retrospective analysis at a predefined time
  - Novel analytical approaches are required for data analysis
    - Filtering out noise
    - Define acceptable false-negative and false-positive rate

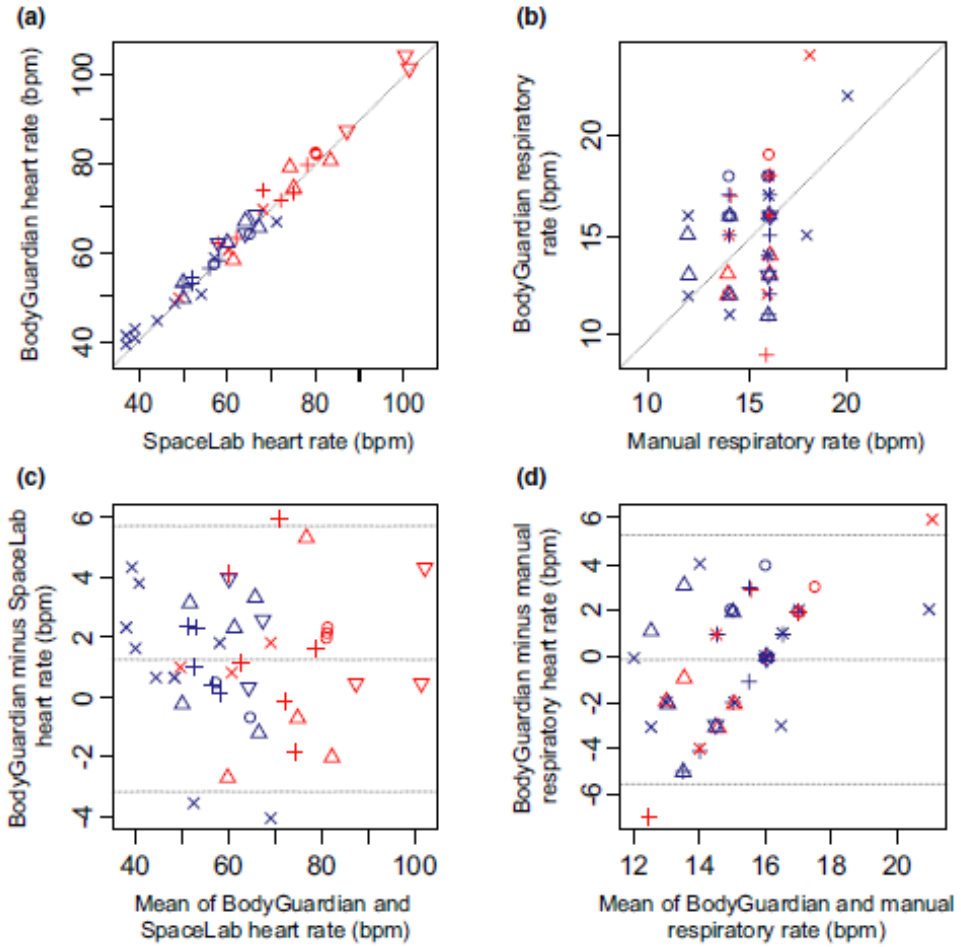
State of Evidence

Equivalence with conventional measurements



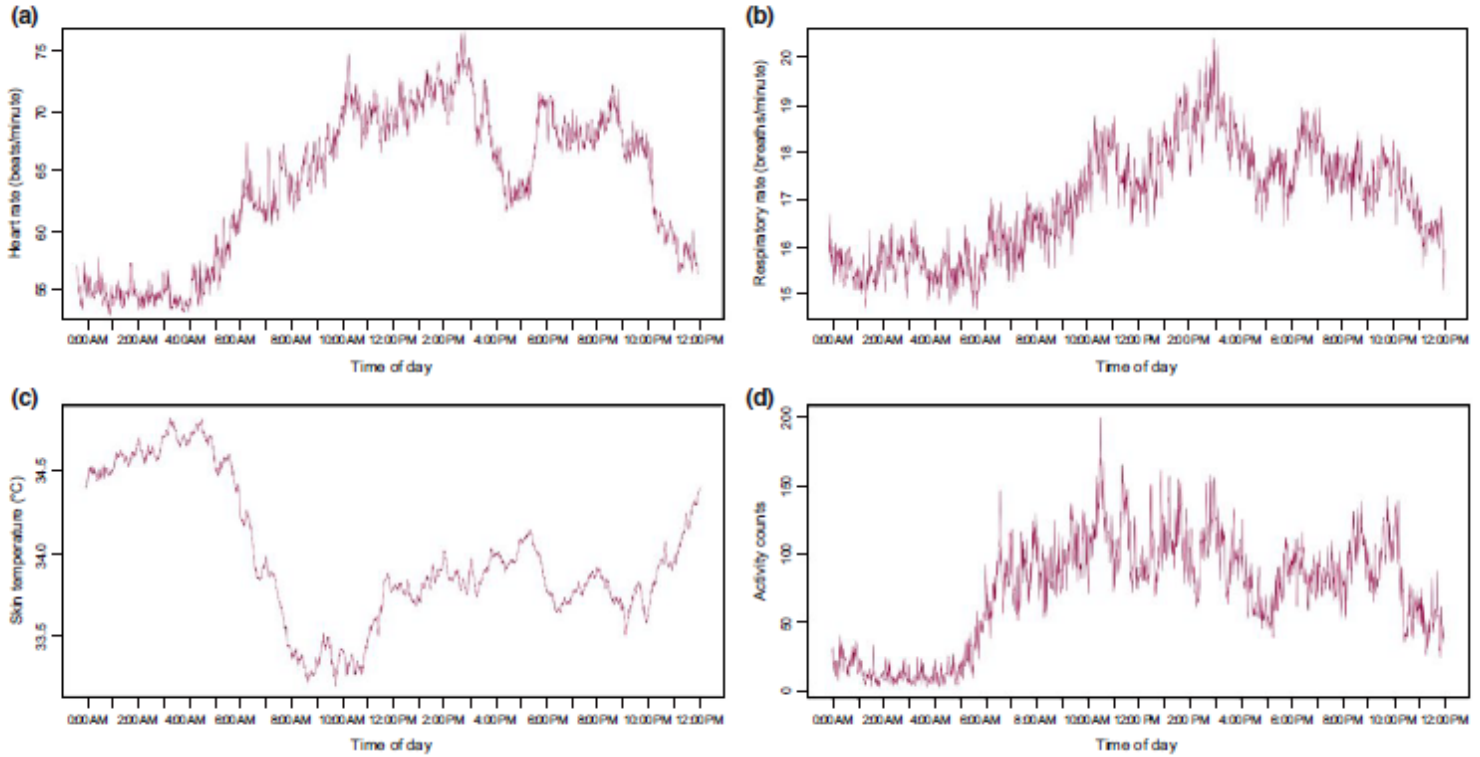
Correlation and limits of agreement

- Comparison to conventional technologies - correlation and limits of agreement
  - conventional 5 minutes resting and supine protocol
- Device to device data comparison is appropriate, a comparison to the manual data collection method is more problematic



https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12673

Face validity of the data – aggregate level



Aggregate data shows clear and consistent diurnal variation patterns

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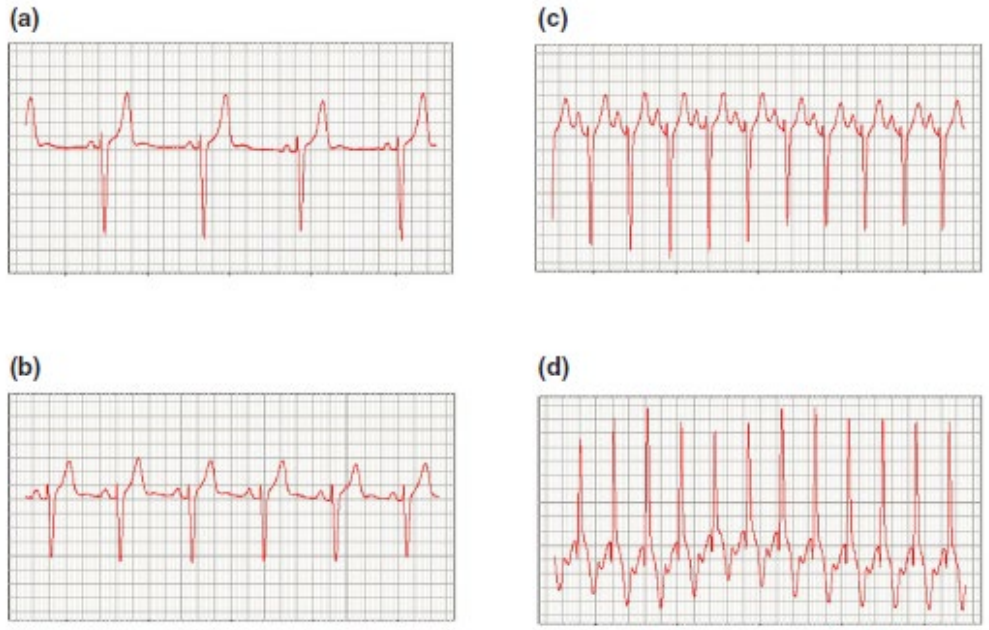
Approach to analytical validation



Reasonableness and physiological validity of the data needs to be evaluated at the individual and trial level

	Gap count	Longest gap (hours)
57001-017	21	1.7
57001-022	113	30.6
57001-024	117	102.3
57001-025	112	64.2
57001-028	100	2.7

Subject ID	% of epochs HR ≥0 and <50 bpm	% of epochs HR ≥50 and <120 bpm	% of epochs HR ≥120 and <150 bpm	% of epochs HR ≥150 and <180 bpm	% of epochs HR ≥180 bpm
57001-017	0.01	98.47	1.52	0	0
57001-022	0.25	96.53	3.2	0.03	0
57001-024	0.01	92.26	7.72	0.01	0
57001-025	19.91	76.55	3.51	0.03	0
57001-028	0	96.95	3.04	0	0

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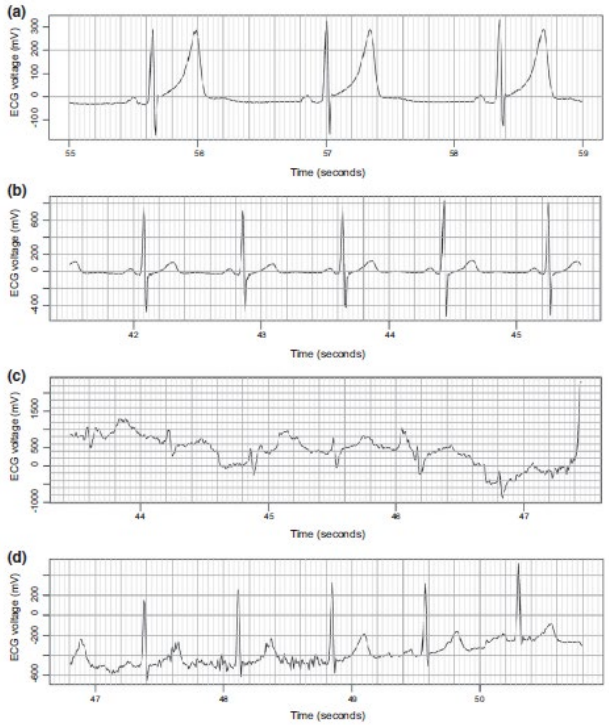
Approach to analytical validation

Non-physiological or any other data representing a potential safety signal requires a follow-up



Subject	Number (%) of epochs with HR > 150 bpm	Number (%) of epochs with HR > 180 bpm
58001_0003	29 (0.02)	13 (0.01)
58001_0007	18 (0.01)	5 (0.00)
58001_0011	9 (0.00)	6 (0.00)
58001_0012	67 (0.04)	6 (0.00)
58001_0015	99 (0.06)	33 (0.02)
58001_0018	258 (0.16)	77 (0.05)

bpm, beats/min; HR, heart rate.

	Gap count	Total gap time (hours)
58001_0003	27	0.6
58001_0007	58	1.5
58001_0011	16	1.5
58001_0012	417	28.3
58001_0015	11	8.3
58001_0018	1345	35.4

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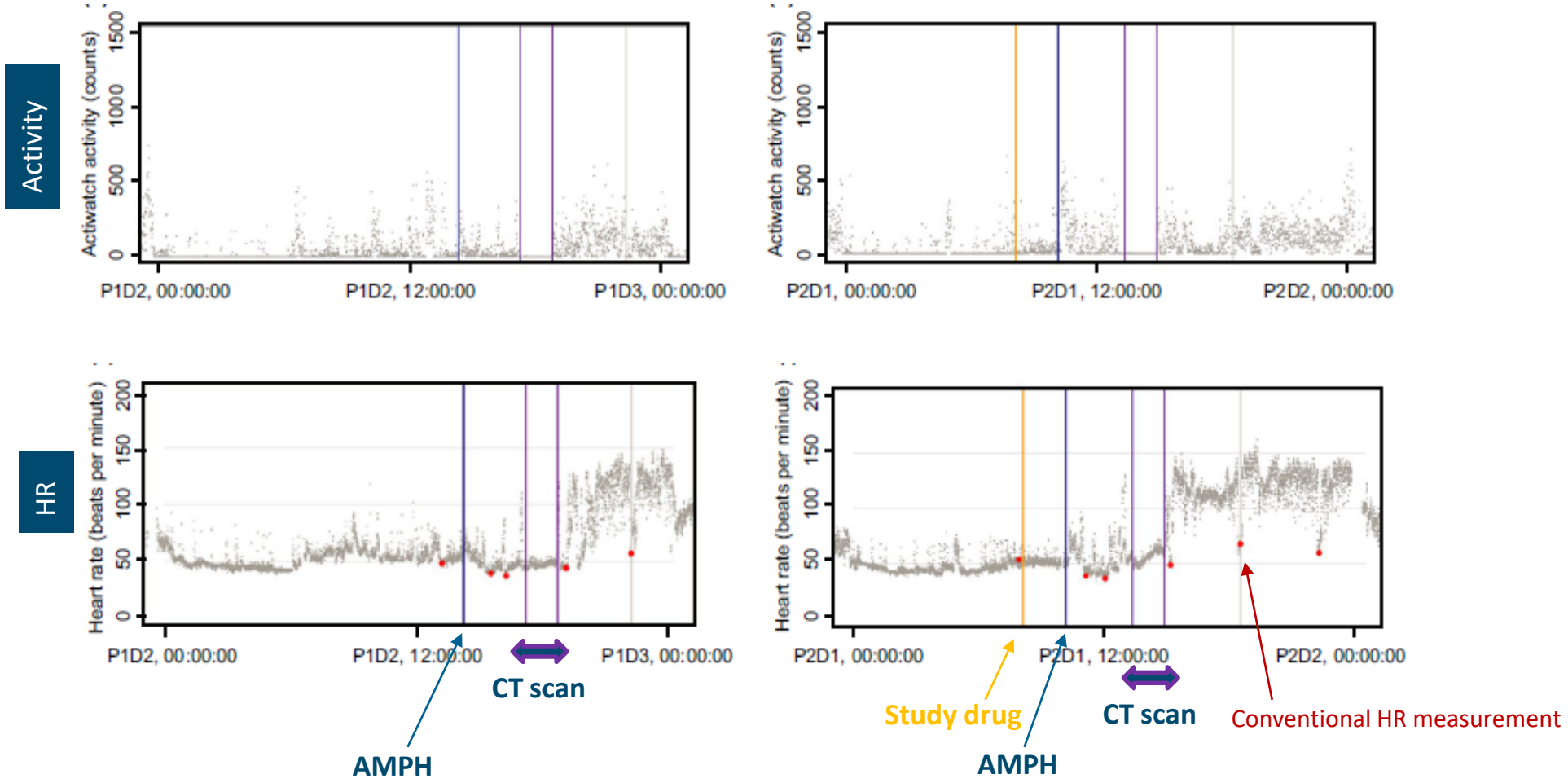
Patient level data



Conventional vital sign measurements at predefined points can miss a signal

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https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12673

Data considerations

- **Ambulatory data will be noisier than the data collected at the resting and supine state**
- **Current studies/results are contingent on**
  - The choice of a device
  - Data processing algorithms
- **Require from device manufacturers**
  - To publish evidence and validation
  - To provide access to raw data
    - To retrospectively detect device/sensor malfunctioning
    - To identify values outside of the calibration range
    - To deal with missing data
- **Understanding the context of adverse clinical events**
  - Patient-reported: cardiac feeling, type of event, extra contextual info
  - Algorithm-derived: sleep/wake, body position (standing/lying)
  - Clinician-derived: review of the signal around the event

Statistical considerations

- **Establish patient-level normative values for HR rhythmicity/variability**
  - Population-level: age/gender/clinical group
  - Use a pre-treatment monitoring to establish patient-level norms
- **Traditional summaries of cardiac burden: Frequency, Duration, Severity, Timing**
- **Novel statistical approaches can help**
  - to maximize the detection of the signal
  - to detect a divergence from the pre-treatment baseline
  - to minimize time taken to review (false positive?) adverse cardiac events
- **Novel statistical approaches include**
  - time-frequency analysis and signal processing
  - functional data analysis (24-hour diurnal patterns)
  - state-transition time-series analysis
  - multi-modal multi-resolution analysis
- **The same methods can be used for safety, efficacy, and treatment effect**
- **Require external validation/replication with independent datasets/studies**

Remote Cardiac Monitoring for Clinical Trials

Sensor Verification for measurement of interest	Analytical Validation of Measure	Clinical Validation	Clinical decision parameters on need
510 (k) cleared devices	Comparison to traditionally accepted measurements: • Correlation • Limits of agreement • Data face validity • Analytical accuracy • Data loss	Traditionally established outcome is measured according to the resting and supine measurement protocol and collected at pre-defined time points	• Replication with independent data sets • Device contingent • Ambulatory reportable range and reference interval • Novel data analytics and statistical approaches

Lessons learned:

- 510(k) clearance does not render devices to be fit-for-purpose for use in clinical trials - validation in the COU is needed
- A more robust framework is needed to assess analytical validity
- Novel analytical approaches are need for ambulatory monitoring

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BACKUP / PANEL SLIDES

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Question and Answer Session

- The initial pilot to establish the framework highlighted challenges. What other elements are needed to establish qualification for remote cardiac monitoring?
- Did the COU achieve the right level of evidence?
- For the technology to be ready for the prime time, what needs to happen to ensure a widespread adoption from the perspective of a broad range of stakeholders?
- Please comment on pros and cons for multiple device integration into a single measurement
  - These pilot studies used 2 ECG devices and a wrist worn actigraphy devices, which were not integrated
- Do you share a concern about introducing patient selection bias because of the technology component, e.g. the need to manage one or more devices and/or cell phones?
- What are the best approaches to handle missing data?

Technology Verification & Validation

Technology = sensor + algorithm

- **What is the sensor type**
  - Single lead ECG patch collecting HR, RR, and skin temperature (Study #1)
    - Study#1: HealthPatch single-lead ECG (HR, RR, and skin temperature)
    - Study#2: BodyGuardian single-lead ECG (HR, RR)
  - Wrist worn actigraphy device: Actiwatch Spectrum Pro

- **How does the algorithm produce the measurement?**
  - Proprietary algorithms/ black box
  - Raw/source data available for both single lead ECG devices (µV/sec and activity counts) - critical for establishing analytical validity