

The Positive “Thorough QT Study” and Continued Development: Practical Issues

Pierre Wicker, MD

Executive Director, Clinical Group Head

Worldwide Clinical Development

Pfizer, Inc

Clinical Development After a Positive TQT Study

Outline of presentation

- **Specific design considerations**
 - Patient selection
 - Dose selection and response
 - Statistical considerations
 - ECG methodology
 - Adverse events
- **General design considerations**

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Key objectives of development program

In the target population

- **Fully characterize dose, concentration and time-relationship between drug and QT interval**
- **Fully characterize relevant adverse event profile**
with particular attention to patients with risk factors for QT-related cardiac arrhythmias

From ICH E14 Guidance, 12May05

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Patient selection

Restrict or expand?

Ensure representativity

Minimize risk

Exclude subjects with risk factors for QT prolongation and TdPs:

- female, baseline QT > 450-480 msec
- CVD, CHF, DM, LQTS
- electrolyte abnormalities
- QT-prolonging medications
- drug-drug/disease interactions

No or minimal exclusion criteria – phase 2b/3 patients representative of target population

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Restrict or expand patient selection?

How to solve the risk vs. representativity dilemma?

- Conduct “all-inclusive” phase 2b/3 studies with rigorous monitoring, especially in high-risk patients
- Exclude high-risk subsets from pivotal studies and conduct separate QT study(ies) in these subsets
- Any combination of above options

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Dose selection and response

Include patients exposed to full range of potential doses and concentrations

- **Therapeutic dose range must be fairly well understood before continuing development**
- **Unlike TQT study, exposures higher than expected maximum therapeutic dose need not be tested**
 - Goal in TQT study is to assess TI prior to exposing large number of subjects
 - Goal in phase 3 is to further characterize TI in a setting relevant to clinical practice

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Dose selection and response

Include patients exposed to full range of potential doses (and concentrations)

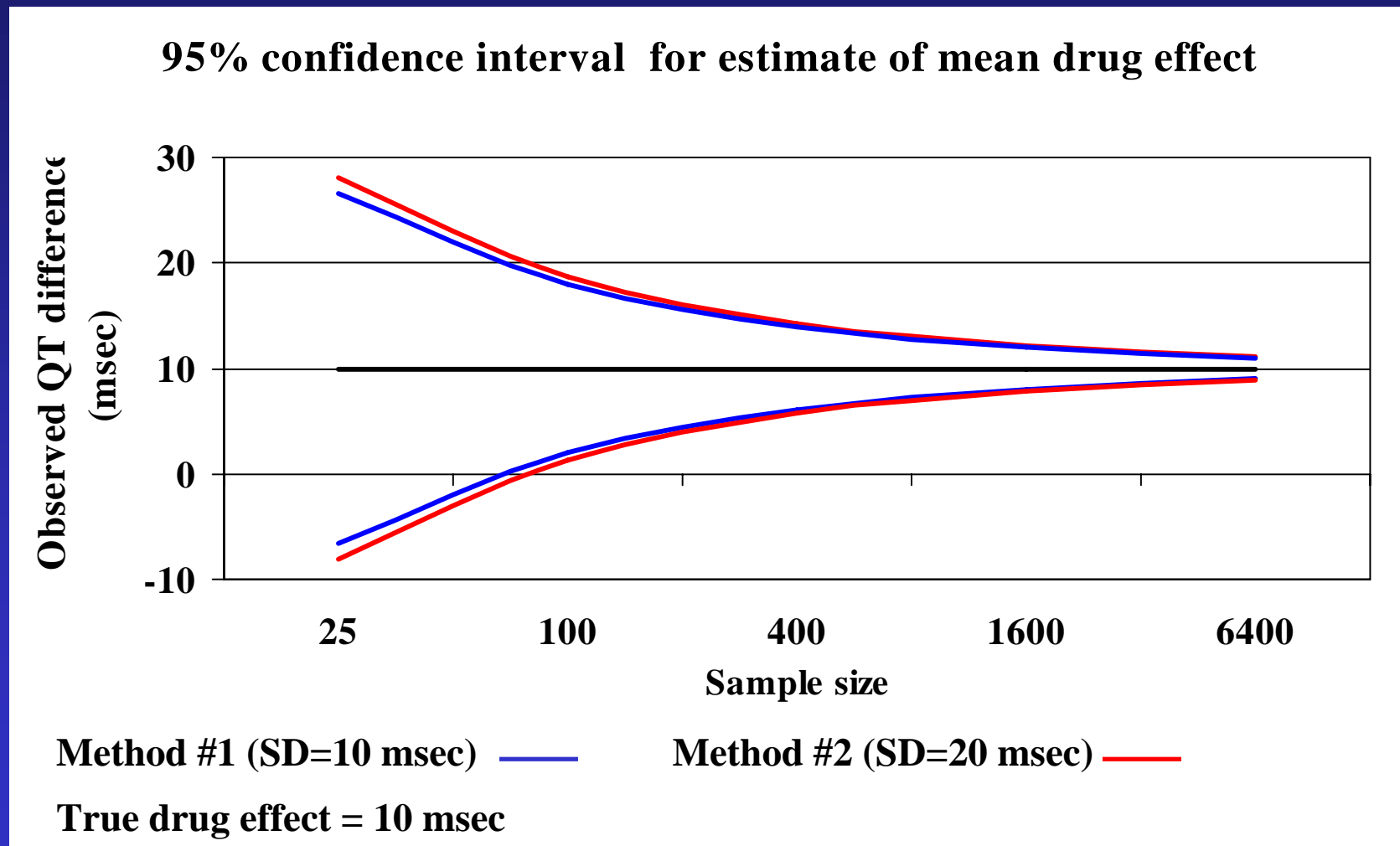
- **The PK/PD relationship in the general population and in drug-drug/drug-disease interactions should be well characterized. This can be done in**
 - Pivotal trial(s) using sparse sampling at C_{max}
 - Separate DD/DDI study(ies)
 - Approach depends on risk-benefit of the candidate and likely representation of at-risk subjects in phase 3 trials

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Sample size and precision of mean QT measurements



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Statistical considerations

Conclusion #1

- **Relatively small studies are more than adequate to precisely estimate mean QT effects**

QT categorical analyses

Sample size and precision of estimate

Theoretical analysis

Threshold value	Outliers*		95% CI**
	n	%	
≥ 450 msec	255	9.11%	225 – 285
≥ 480 msec	28	1.00%	18 – 38
≥ 500 msec	4	0.14%	0 – 8

* Number (n) and proportion (%) of patients with QTc \geq threshold value assuming a normal distribution (410 \pm 30 msec); N = 2800

** rounded to nearest integer

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Statistical considerations

Conclusion #2

- **Large databases are required for categorical analyses.**
 - Formal statistical analyses usually not performed (underpowered)
 - Concurrent placebo group is critical for comparisons of observed frequencies in outlying categories
 - Will usually detect only a trend unless the drug effect is substantial or the sample size unrealistically large
- **When a drug effect is present, the main value of categorical analyses is not to quantify the risk but to identify patients potentially at risk**

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QT measurement methodologies

Terminology

	Central lab	ECG format	Fiducial marks	QT interval verification	QT interval calculation
Manual					
- fully manual ¹	Yes	<i>paper</i>	<i>technician</i>	<i>cardiologist</i>	<i>cardiologist</i>
- computer-aided ²	Yes	digital	computer	cardiologist ³	computer or cardiologist
Semi-automated ⁴	No	digital	computer	site reader	computer
Automated ⁵	No	digital	computer	n/a	computer

1. Historical interest – no longer used

2. The majority of QT intervals are manually read; the computer is only used as a tool to facilitate initial placement of fiducial marks.

3. May involve two steps (usually technician and cardiologist).

4. A trained reader at the site adjusts the placement of fiducial marks **only** in case of significant computer errors. The computer is the primary measurement tool and most QT intervals are machine read.

5. No human intervention. All QT intervals are machine read.

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ECG methodology

Manual or automated measurements?

- **Automated methods**
 - Are at least as reliable as manual methods in normal volunteers
 - But have not been validated in patients

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ECG methodology

Manual or automated measurements? Ct'd

- **In patients, computer algorithms may not measure the QT interval reliably in the presence of abnormal T-wave morphology**
 - When the T-U wave morphology remains normal, automated measurements should be as reliable as manual methods
 - When changes in T-U wave morphology are seen or expected, manual methods are preferable

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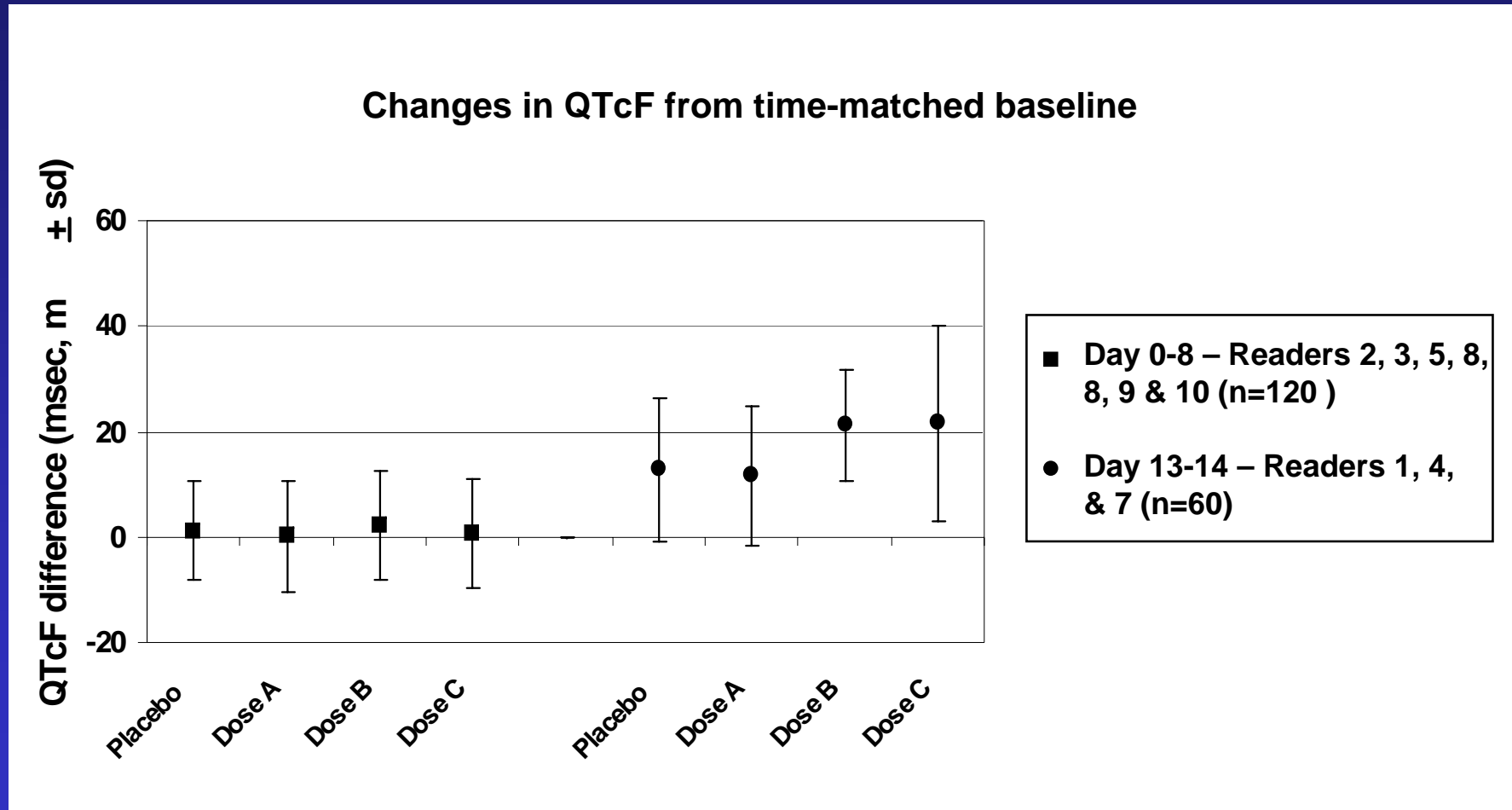
ECG methodology

Phase 2b/3 specific issues

- **Increased measurement variability is a potential issue in large phase 3 programs**
 - May result from using
 - multiple readers (manual)
 - different machines (automated)
 - Other sources of variability (rest, food, etc..) may not be as well controlled as in a TQT

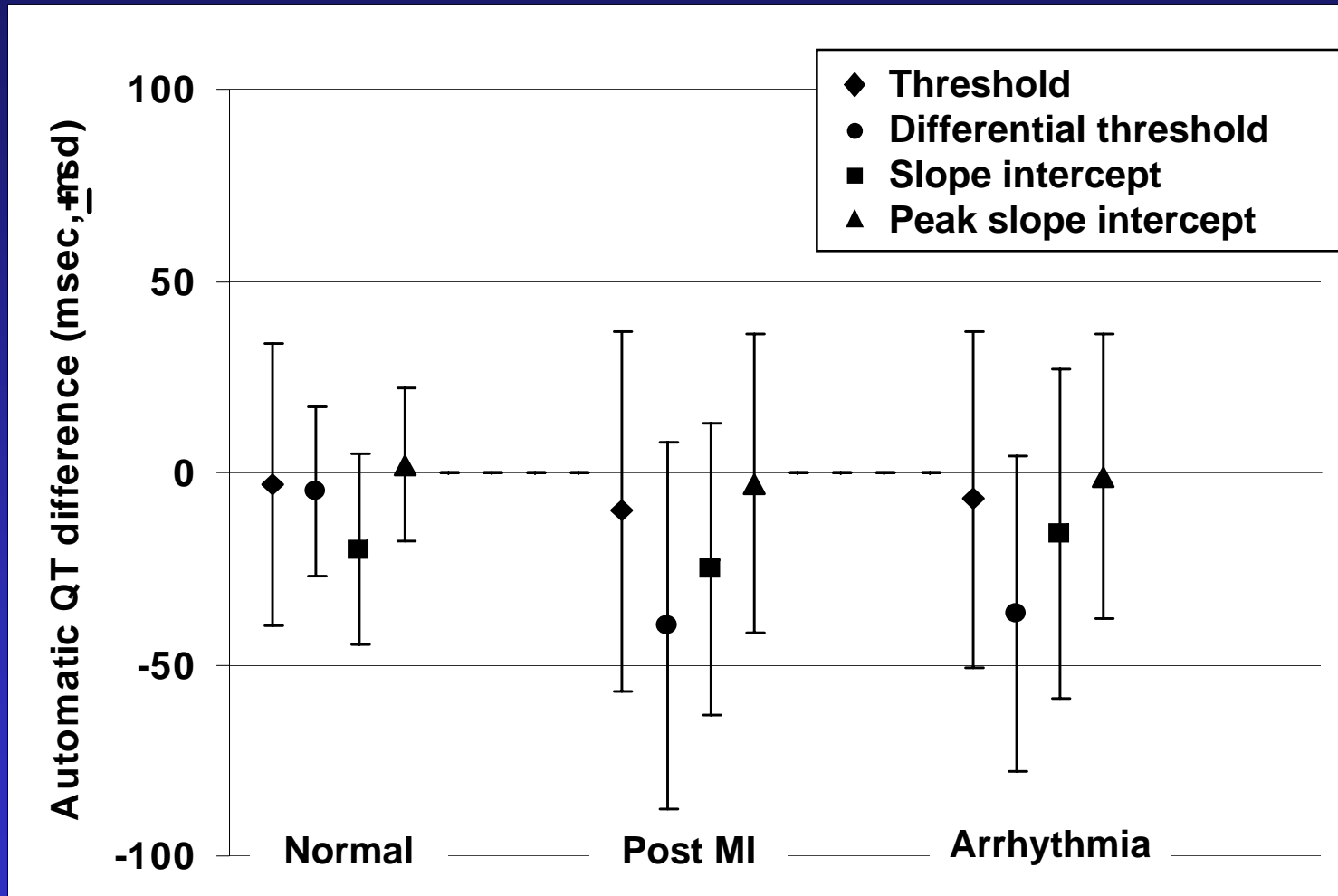
Reproducibility of manual QT measurements

Inter-reader bias and variability



Automatic QT measurements

Between-algorithm differences



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ECG methodology

Phase 2b/3 specific issue

- **Increased measurement variability is a potential issue in large phase 3 programs**
 - May overestimate the proportion of outliers in categorical analyses

QT categorical analyses

Impact of increased measurement variability

Theoretical analysis

	Method #1	Method #2
True QT distribution*		
- control	400 \pm 30	400 \pm 30
- active	415 \pm 30	415 \pm 30
Measurement error	0 \pm 10	0 \pm 20
Observed % of outliers (QT \geq 500 msec, active minus control)	0.28%	0.64%

All values in msec (m \pm sd).
* Assumptions:
- normal distribution
- mean drug effect = 15 msec, no effect on QT distribution

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ECG methodology

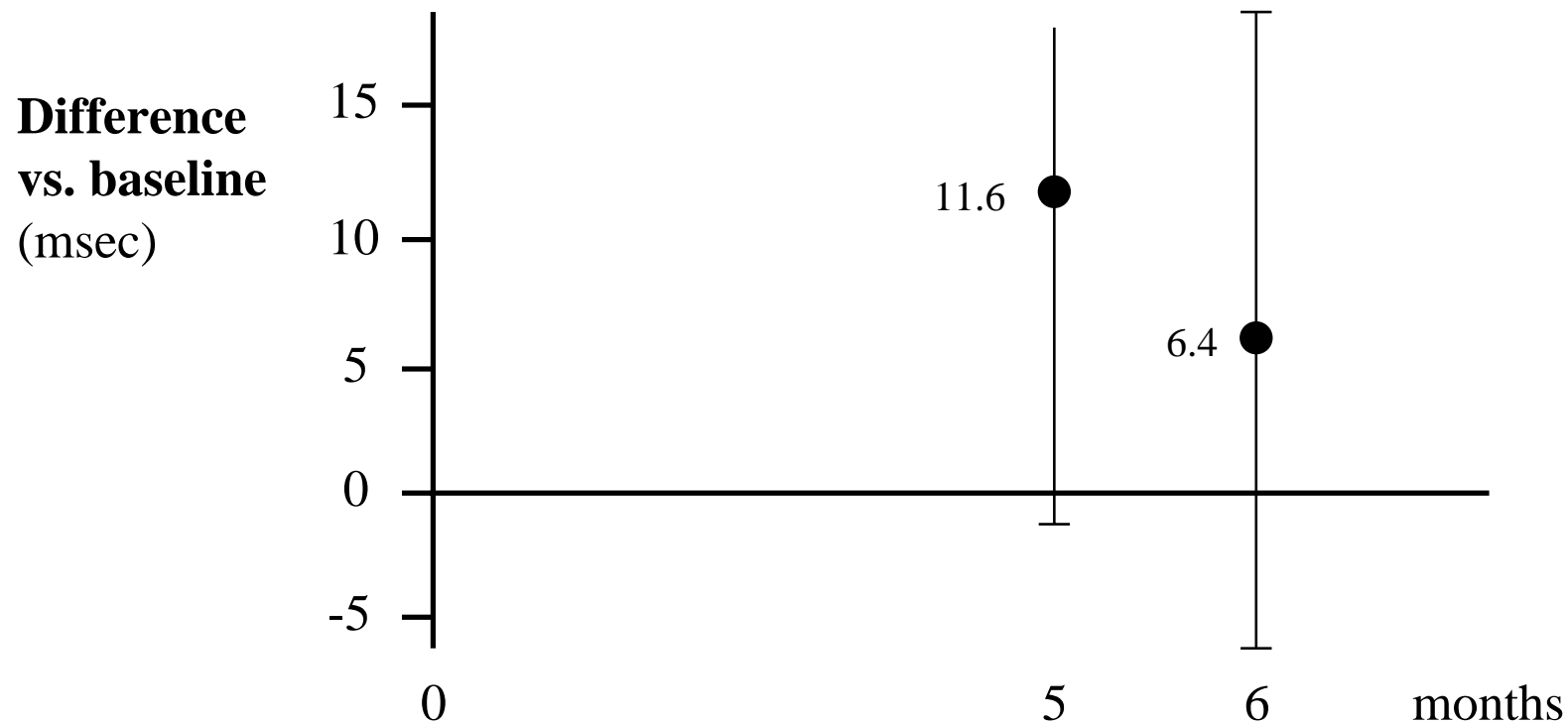
Phase 2b/3 specific issue

- **Increased measurement variability is a potential issue in large phase 3 programs**
 - May result in biased estimates of proportion of outliers in categorical analyses
 - What can be done to reduce variability?
 - the same methodology/reader is used for each patient
 - ECGs from a single patient are batched and read within a reasonably short time frame (to minimize time-dependent shift in QT interval measurements)

Manual Measurements of the QT Interval

Time-dependent intra-observer bias

Differences in repeated measurements performed by the same two readers at 5 and 6-month intervals



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Adverse events – What do we need to capture?

Relevant adverse events

- **Include marked QT/QTc prolongation (> 500 msec) or serious CV events suggestive of a cardiac arrhythmia**
 - syncope, seizures, sudden death, TdP, VT, VF
 - identify risk factors that might have contributed to the event
 - provide narratives (even if AE is not serious)
- **Include premature discontinuations or dosage reductions due to QT prolongation**
- **Provide adverse event analyses from “at-risk” subsets**
 - electrolyte abnormalities
 - underlying CV disorder (e.g., CHF)
 - drug-drug or drug-disease interactions increasing exposure
 - female patients, age < 16 and > 65 years

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Adverse events – Practical considerations

- **Prospectively design Case Report Forms and database to accurately capture and analyze the required safety data**
 - relevant demographics and underlying diseases
 - concomitant medications
- **Train and monitor research site personnel to ensure safety events are properly recognized, reported and managed**
- **Consider using the Event Classification Committee and/or DSMC to adjudicate and monitor relevant AEs**

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- **General design considerations**

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General design considerations driving the development strategy

- **What is the magnitude of the early QT signal?**
 - Guides early patient selection and ECG evaluation
 - Substantial signal may require staged strategy to minimize risk
- **Was the PK/PD profile well characterized in early development?**
 - Entire concentration range tested? Major DDIs investigated?
 - Guides dose selection, ECG timing and DDI studies

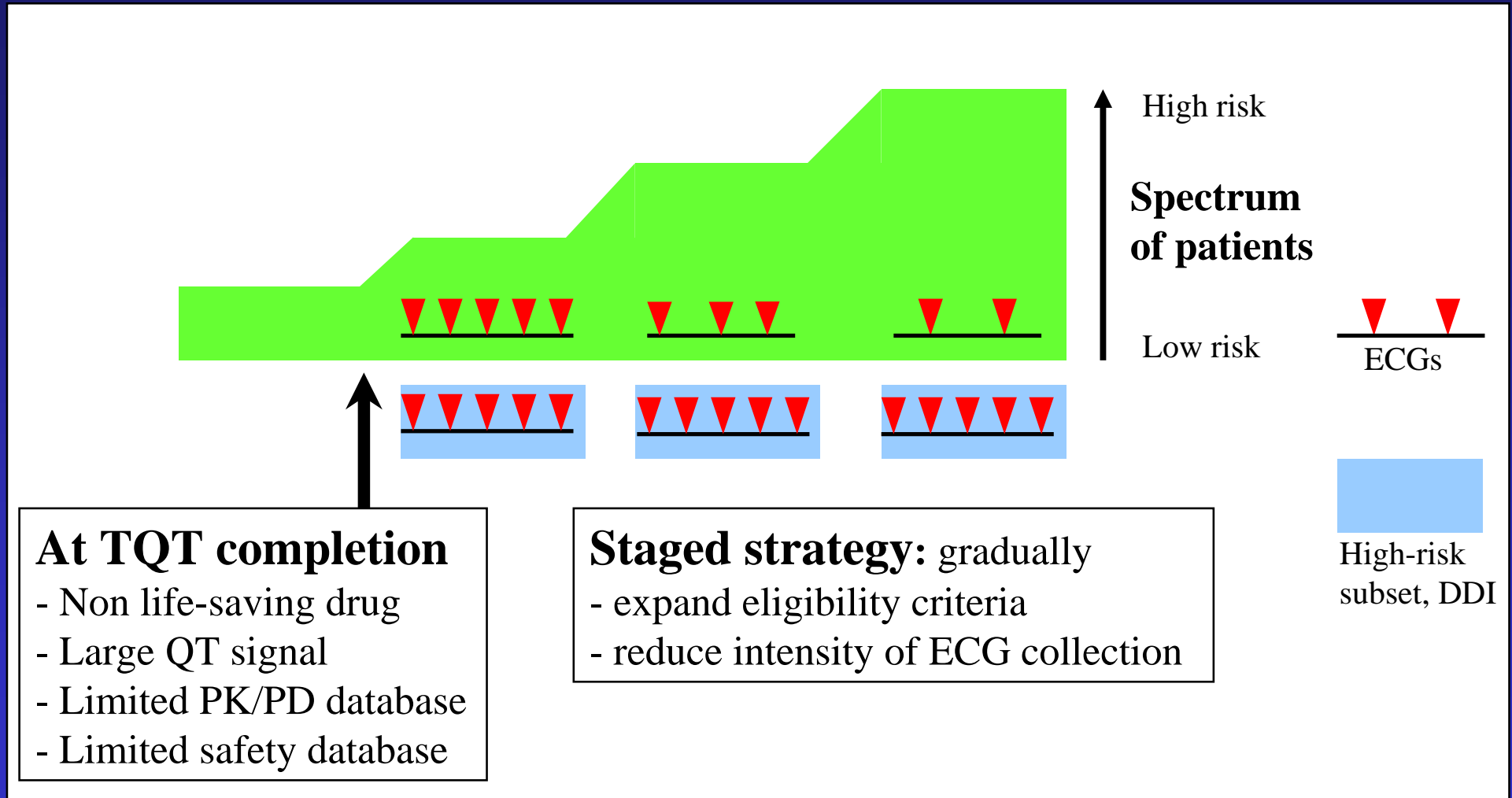
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General design considerations driving the development strategy

- **Was the patient risk profile well characterized in early development?**
 - Guides early patient selection and program staging
- **Is the compound a life-saving medication?**
 - Guides speed of program
- **Are there other medications available and what is their effect on QT?**
 - Guides the need for comparative studies

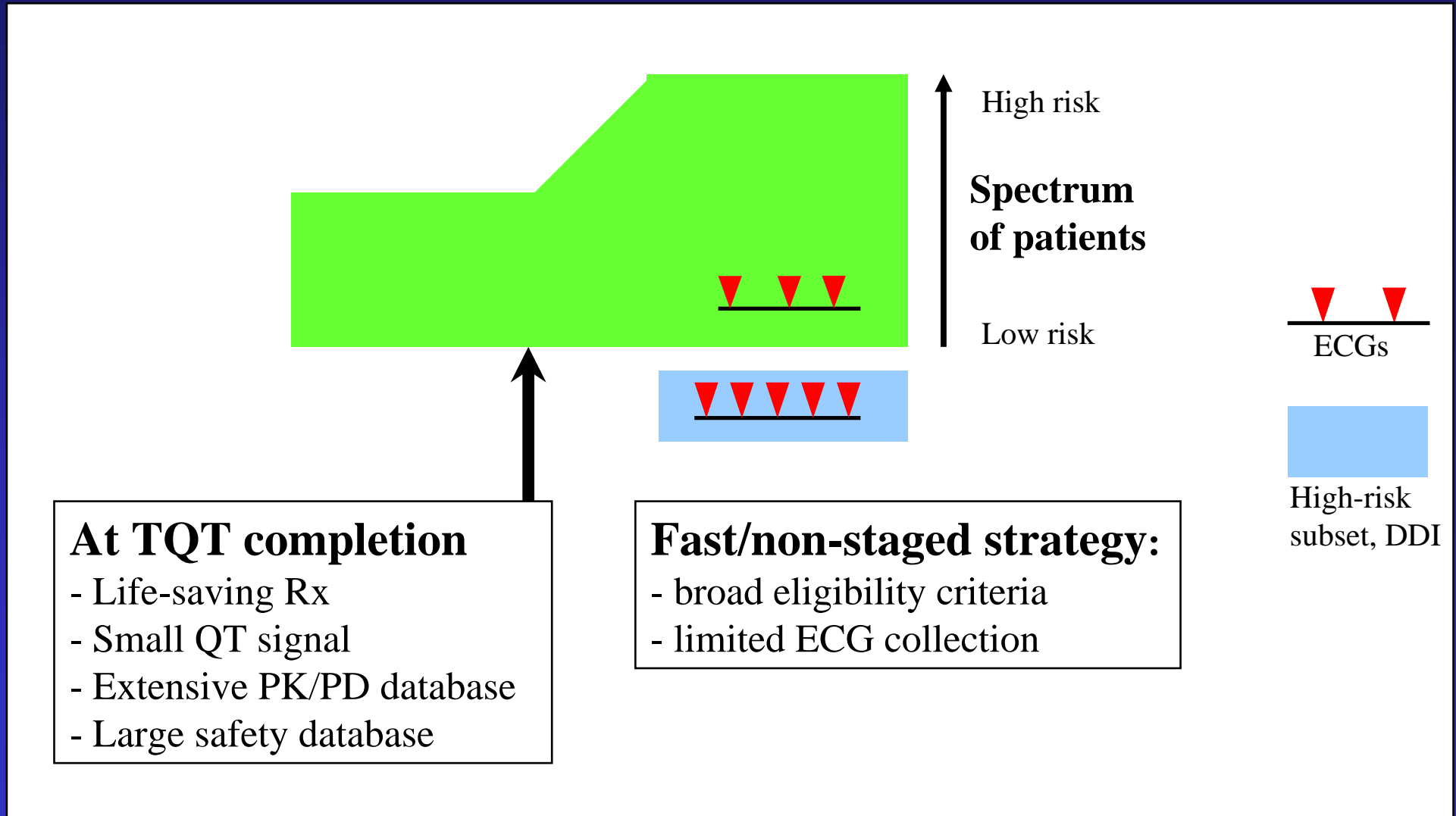
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General design considerations – Scenario #1



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General design considerations – Scenario #2



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Conclusions

- **A rigorous evaluation of the QT interval during early development is critical to guide the phase 2b/3 strategy**
- **Regulatory input should be sought prior to commencing the phase 2b/3 program**

Acknowledgments

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