Clinical Trials in Pregnant Women

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Veramed Limited

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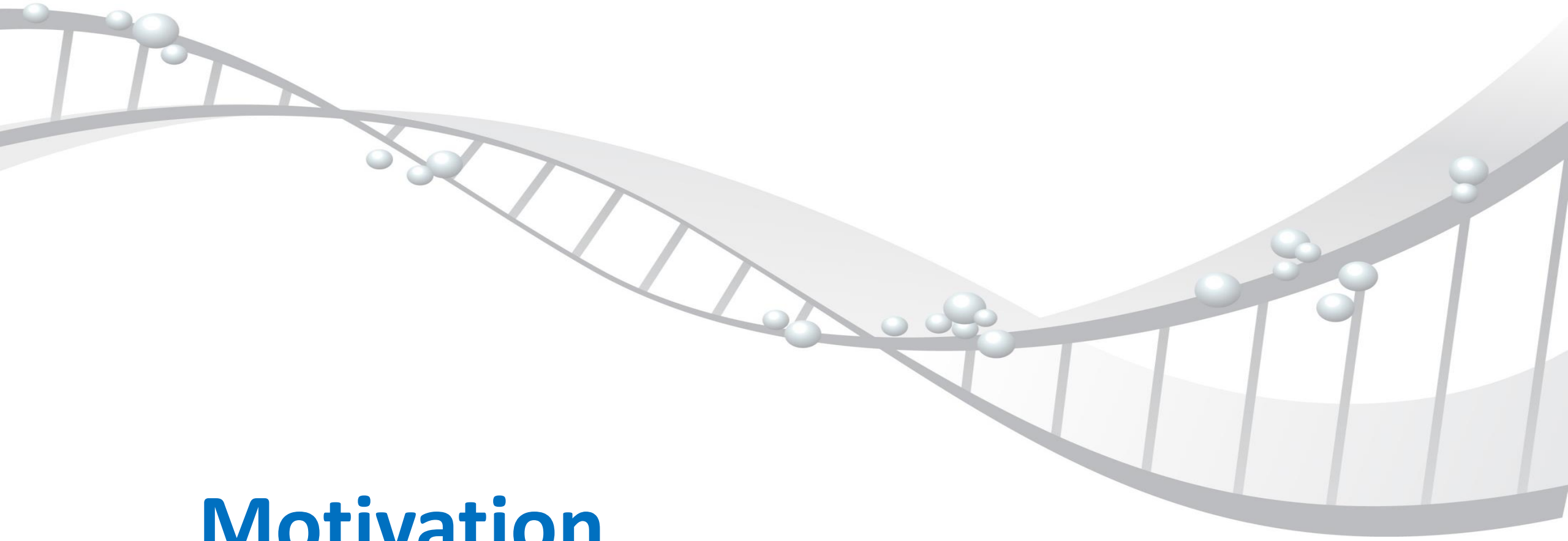

Motivation

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"In the absence of data, the usual adult dose is typically prescribed for pregnant women. Because of the physiologic changes inherent in pregnancy, the result can be substantial under dosing, or, in some cases, excessive dosing."

- FDA Guidance, April 2018

Physiological Changes during Pregnancy

- Hormonal changes
- Increased breast size
- Cardiac output increases
- Lower iron levels
- Blood pressure can drop during first trimester
- Oedema (swelling)
- Weight gain
- Increased kidney and ureter size
- Respiratory condition exacerbation

Historical Concerns

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Thalidomide 'caused up to 10,000 miscarriages and infant deaths in UK'

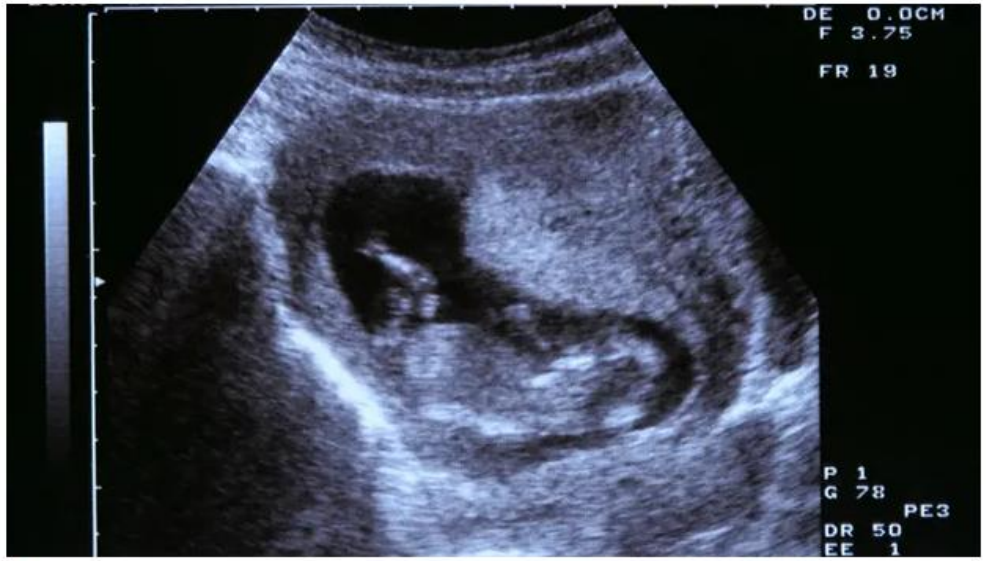
Former head of the Thalidomide Trust says many mothers would not have known drug was the cause of miscarriage or stillbirth

▲ A thalidomide survivor in therapy at Chailey Heritage in East Sussex. Photograph: Jane Bown

The thalidomide scandal may have led to 10,000 miscarriages, stillbirths and infant deaths in Britain, according to the former director of the trust that oversees payments to hundreds of people disabled by the drug taken by their

Paracetamol use in pregnancy may harm male foetus, study shows

Researchers investigating reproductive defects in baby boys identify possible link between low levels of testosterone and paracetamol intake



▲ Ultrasound scan of a foetus. A study involving mice discovered paracetamol lowered testosterone levels over the course of a week. Photograph: Stockfolio/Alamy

Hundreds in baby drug scandal

By Natasha Wallace Health Reporter
November 20, 2007 — 11.00am

HUNDREDS of women have been given a drug that may be implicated in serious birth complications, but the state Health Department is refusing to release details on how many hospitals have used the controversial method of inducing labour.

DRUG SCANDAL What was the Primodos pregnancy test drug, what birth defects is it alleged to have caused and how many women used it?

> The oral hormone-based test was given to women by their GPs in the 1960s and 1970s

Pregnant women who need medications face a risky guessing game. A federal task force is now trying to help

By MEGAN THIELKING @meggophone / DECEMBER 5, 2017

14,000 pregnant women in France took 'birth defect drug'

Dépakine has been linked to an increased risk of various congenital defects. File photo: AFP

Disabilities caused in babies by epilepsy drug a 'scandal'

By Zack Adesina
BBC Inside Out, London

22 January 2018 Shar

Potential Research Questions

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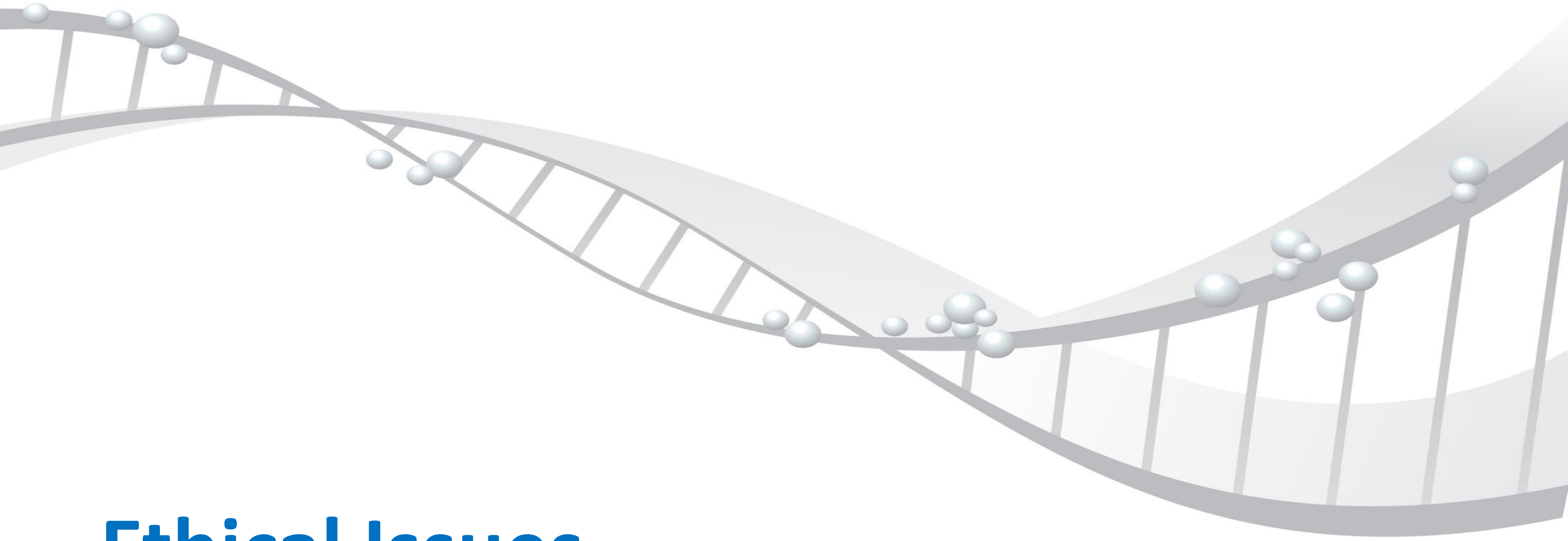
- Is the drug safe for the mother during pregnancy?
- Is the drug safe for the baby during pregnancy?
- Are the pharmacokinetics affected by pregnancy; does the dose need to be adapted?
- Post-partum – is the drug ingested by the baby through breast milk?
- Could taking this drug improve the health of the baby?
- Could the drug help with pregnancy side effects?



Ethical Issues

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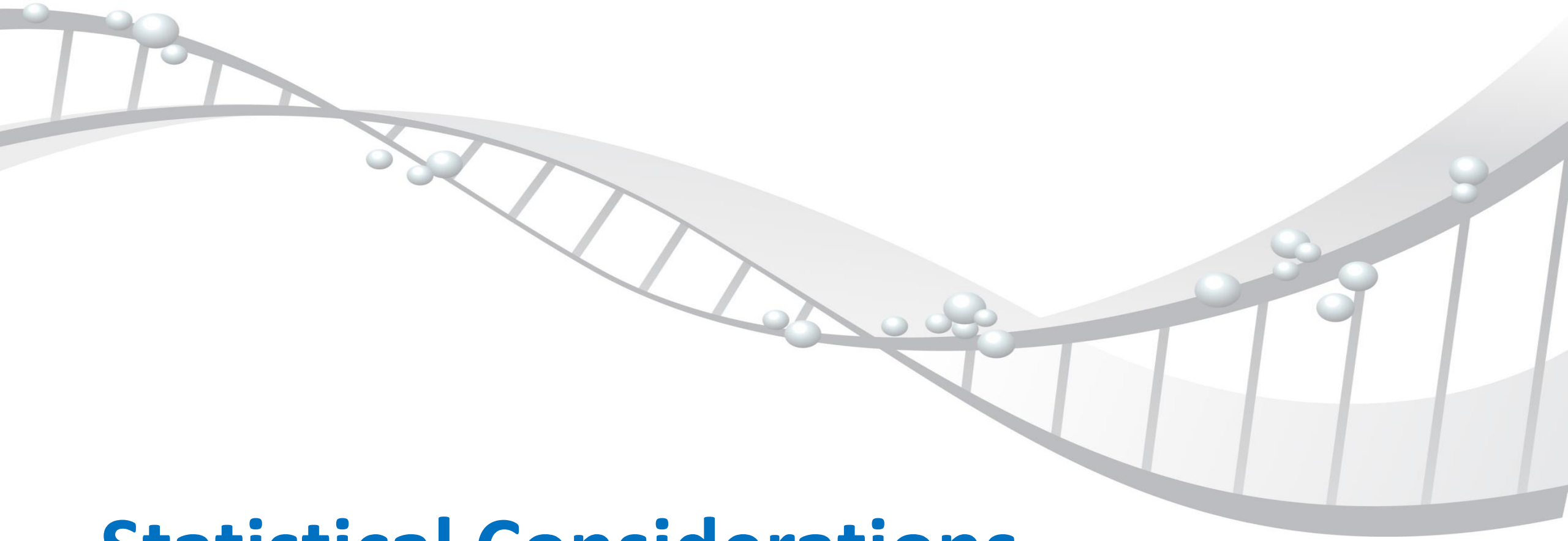
Reasons **not** to include pregnant women in trials:

- Knowledge on how drugs affect the foetus is minimal
- Safety risks are much higher
- Consent is more complex, in some cases paternal consent is also needed
- Pregnant patients require more monitoring and safeguarding

Ethical Issues

Reasons to include pregnant women in trials:

- Unethical to prescribe drugs to pregnant women, when little/no data is available
- Could result in future trials of the drug having more relaxed inclusion criteria
- Improve dose selection in pregnant women
- Health benefits for both mother and baby can be explored



Statistical Considerations

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Design recommendations:

- Longitudinal (to get data across all trimesters)
- Ideally baseline data would be collected, so that each woman can serve as her own control
- MMRM approach is recommended
- 4-week windows for measurements are specified within each trimester

Trimester	Month	Week
	One	1-4
	Two	5-8
	Three	9-13
	Four	14-17
	Five	18-21
	Six	22-26
	Seven	27-30
	Eight	31-35
	Nine	36-40

Example Study Design

- Population: Pregnant women taking long-term medication for chronic back pain

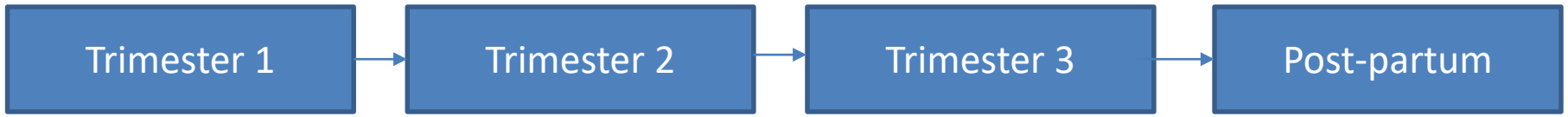
- Research Questions: Is it safe to continue to take this medication?

  Would increasing the dose improve efficacy?

Example Study Design

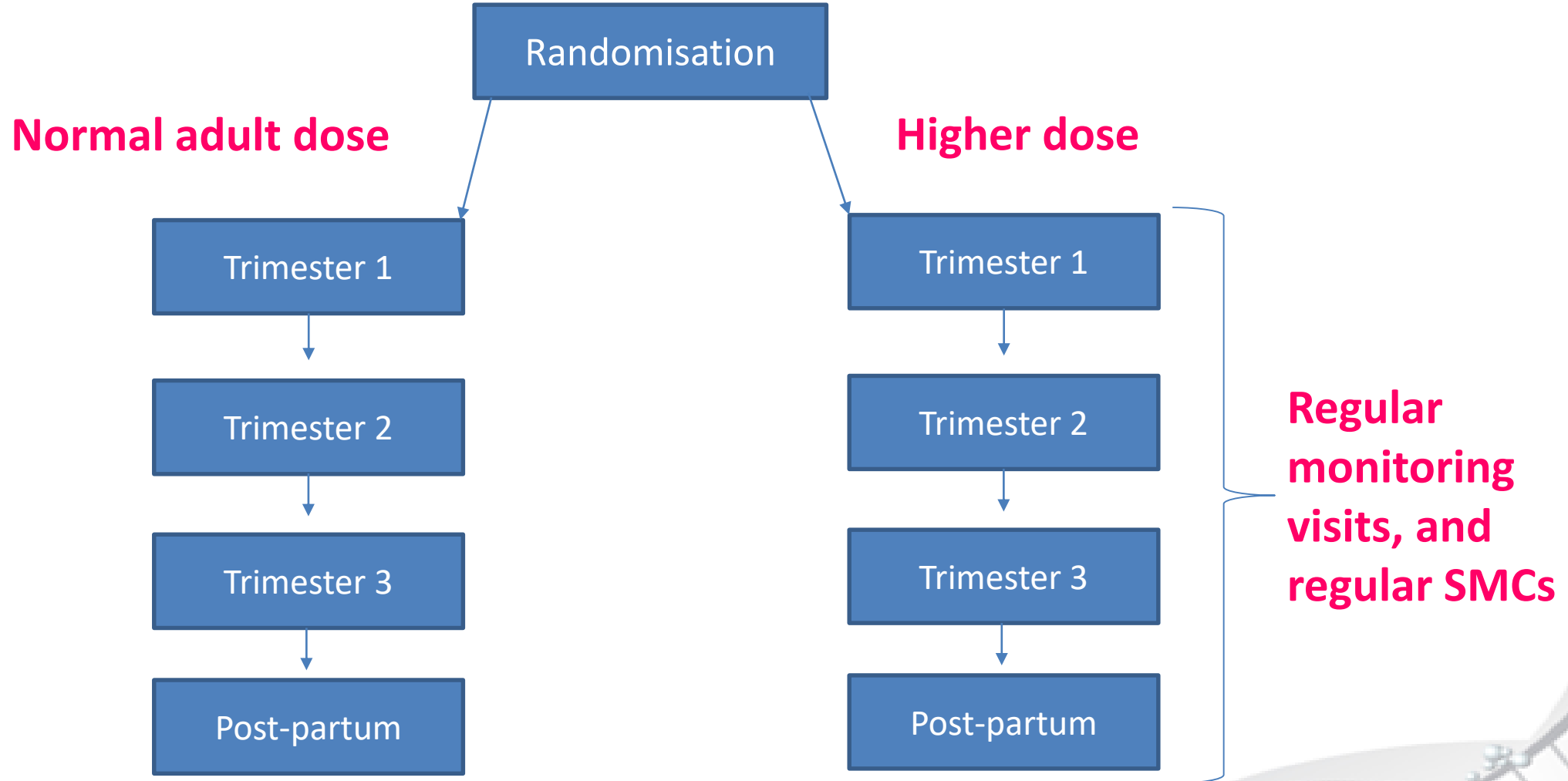
- Trial 1: Safety

- Follow the normal adult dosing schedule, with continuous recording of adverse events
- PK parameters calculated within each trimester and compared to baseline



Example Study Design

- Trial 2: Should the dose be adapted?



Summary

- Although it may seem unethical to test drugs on pregnant women, excluding them is also a problem
- Dose adjustments in pregnancy need to be explored
- More research is needed in terms of how to best perform pregnancy trials

Questions?