# An ongoing adaptive PII/III trial with dose selection

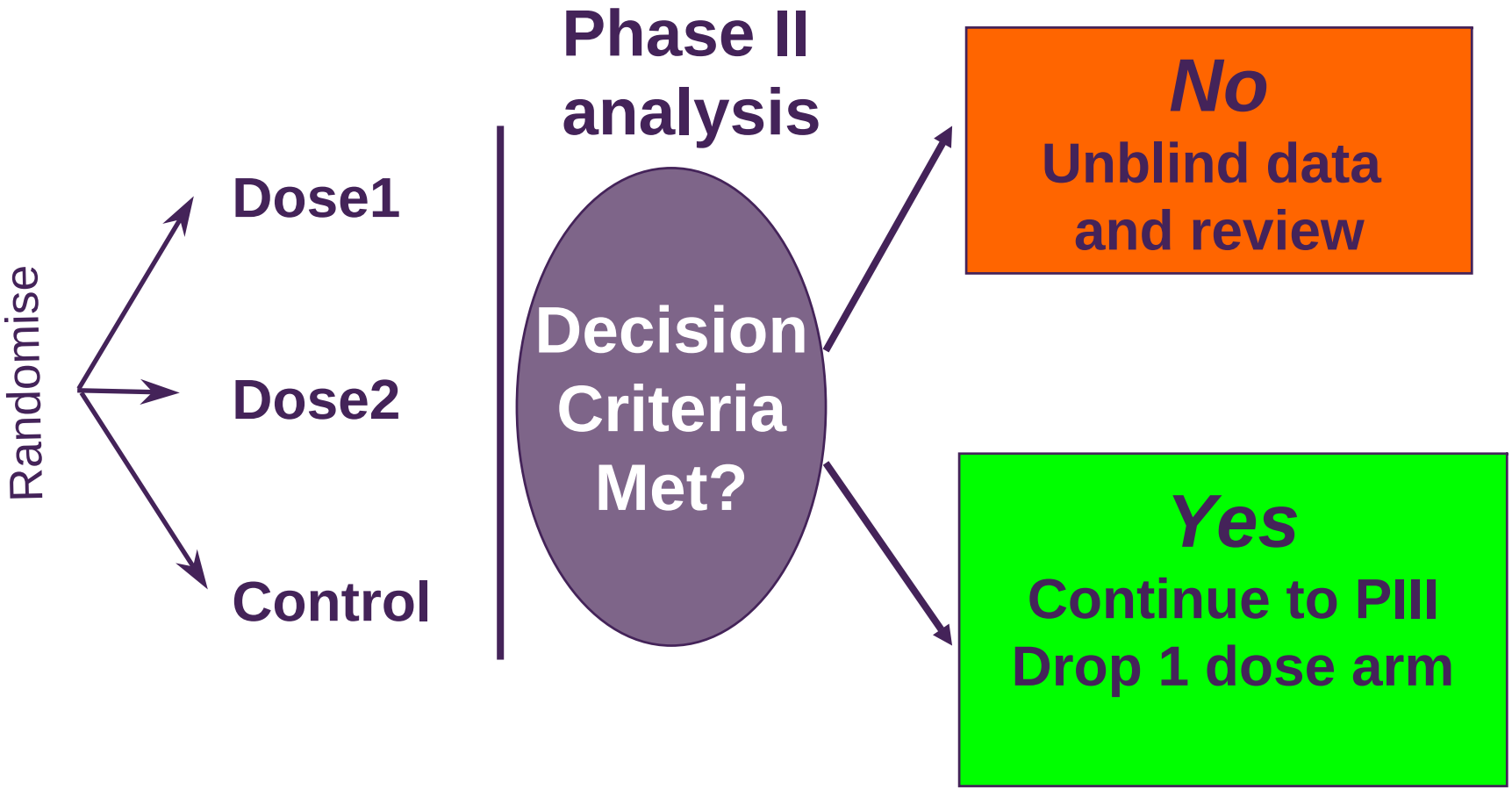
## A pragmatic solution for a development programme

Andrew Stone 14th Dec 2007

# Background & rationale

- AZ Case Study in an area of high unmet need
- Desire to develop important new medicines efficiently
- Want to make sure the opportunity is taken to minimise patient exposure, and optimise resources of AZ and trialists, if the agent is insufficiently effective
- Optimise dose selection
- Trial design created to meet these needs
  - Did not know it would be called an Adaptive design BUT
  - Naturally only too aware of data access issues and control of Type I error

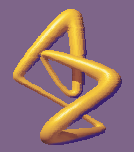
# Adaptive, seamless PII/III design with dose selection



# PII data access

- End of phase II (EOPII) GO criteria pre-defined
- An IDMC performing the EOPII analysis
  - The EOPII criteria are documented in an IDMC charter that only AZ and IDMC have access to
- Should the criteria be achieved, PII results will not be disclosed to either AZ or investigators
- Our philosophy is that if results are good, AZ and investigators do not need to know just how good

# EOPII GO criteria definition



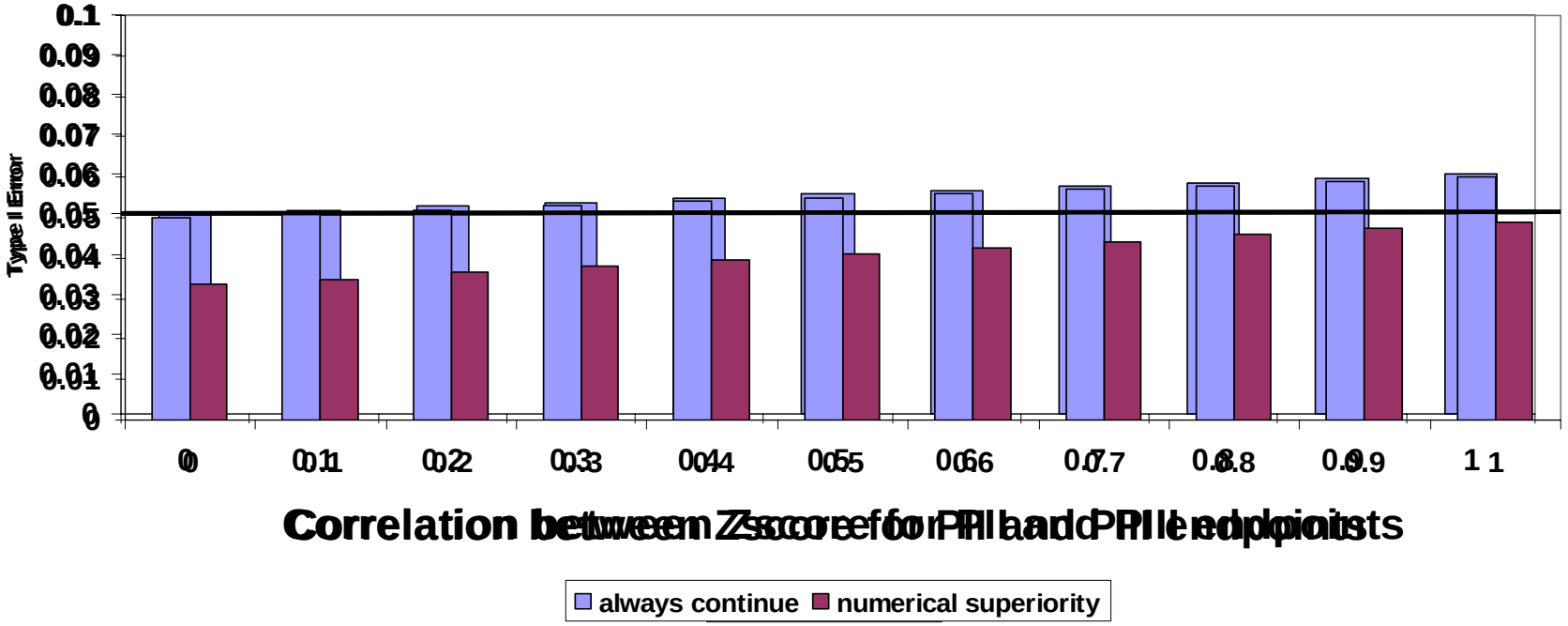
- Lack of PII access puts a premium on a thorough understanding and sponsor acceptance of GO/NO GO criteria
- Necessarily a lengthy and detailed process to define
- Used predictive power methodology to guide approach
  - A Bayesian approach but crucially one where the prior is based on data and not opinion

# Phase III data analysis

- A single test of continued dose vs control group
  - Includes PII patients
  - Equal weight is given per patient
  - No- p-value combination or aggregating of doses
- Phase III analysis approach fixed in the protocol including factors that stratify the analysis

# Type I error considerations for PII/III trials with dose selection

Example where PII analysis performed at 5% of PIII events



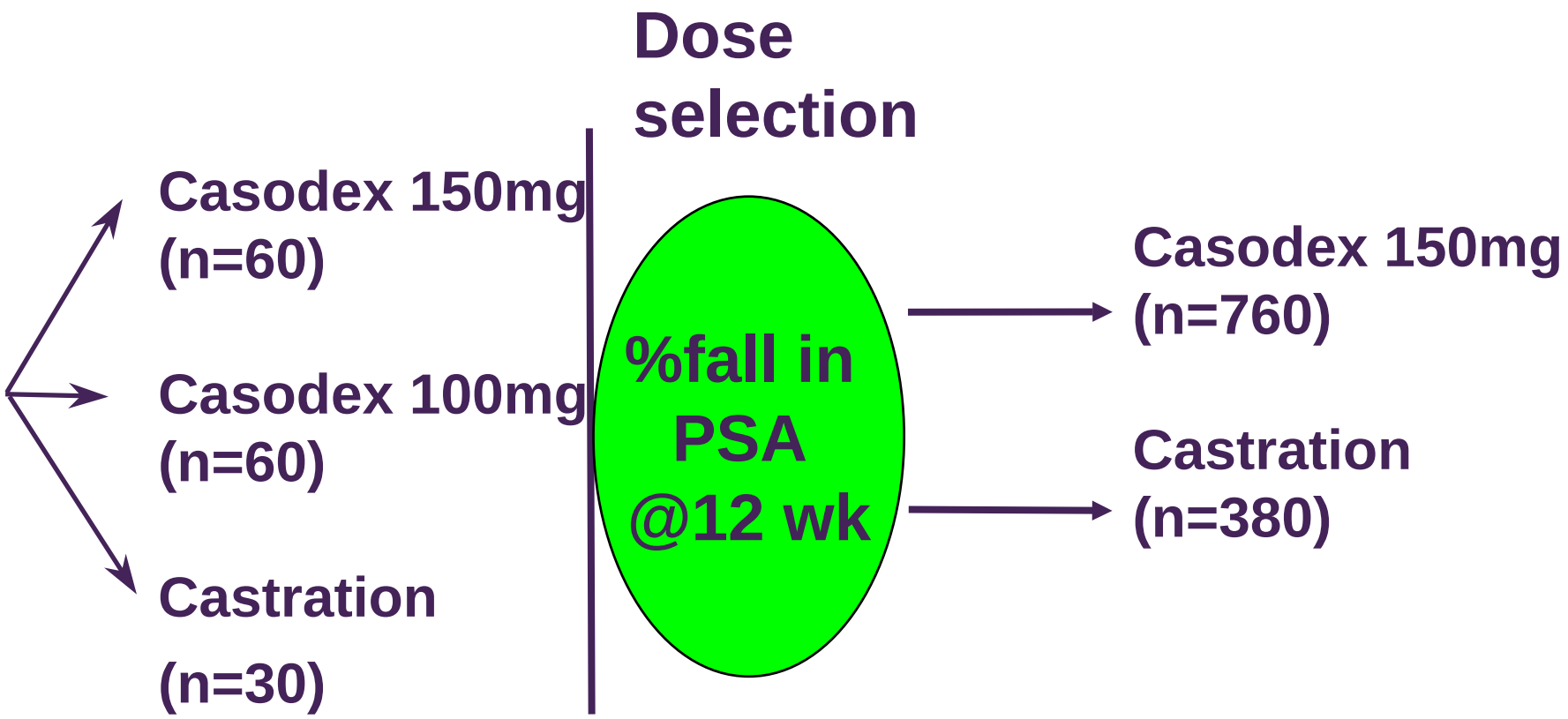

- Final significance level requires minimal adjustment even with studies without futility analyses and a strong correlation between PII and PIII endpoints

Stallard and Todd SIM 2003 22:689-703 & Todd and Stallard DIJ 2005 39:109-118

# Advantages of programme

- Provides the potential to deliver the new therapy to patients, in an area of high unmet need, with significant time savings
- Minimises patient exposure, and optimises resources AZ and trialists, if new therapy insufficiently effective

# None of this new!
# 1992 Casodex Adaptive design




- Pre-planned dose selection on PSA
- Data from patients recruited prior to dose selection included in final efficacy assessment of Overall Survival

# Summary

- Future role of Adaptive designs at AZ
  - Will be considered for high potential compounds
  - Operationally complex
- In selection situations such as this can highly be advantageous to sponsors and patients alike