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Treatment changes in cancer clinical trials: design and analysis

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Statistical methods and designs in clinical oncology
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Plan

1. Treatment changes – example and scope
2. Estimands – what are they and why do they matter?
3. Analyses – a toolkit
4. Designs – some important suggestions

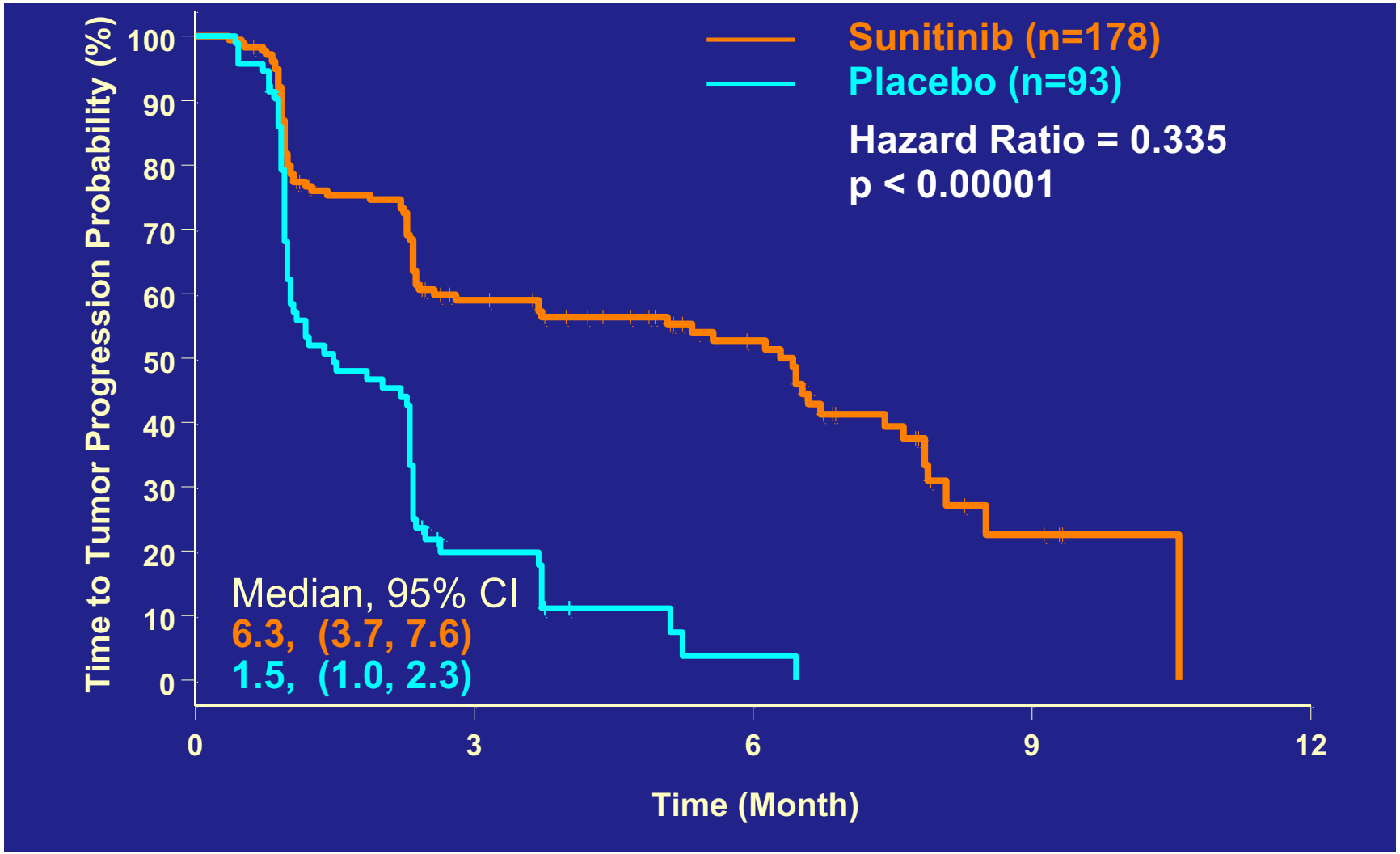
Plan

1. **Treatment changes**
2. Estimands
3. Analyses
4. Designs

Sunitinib trial

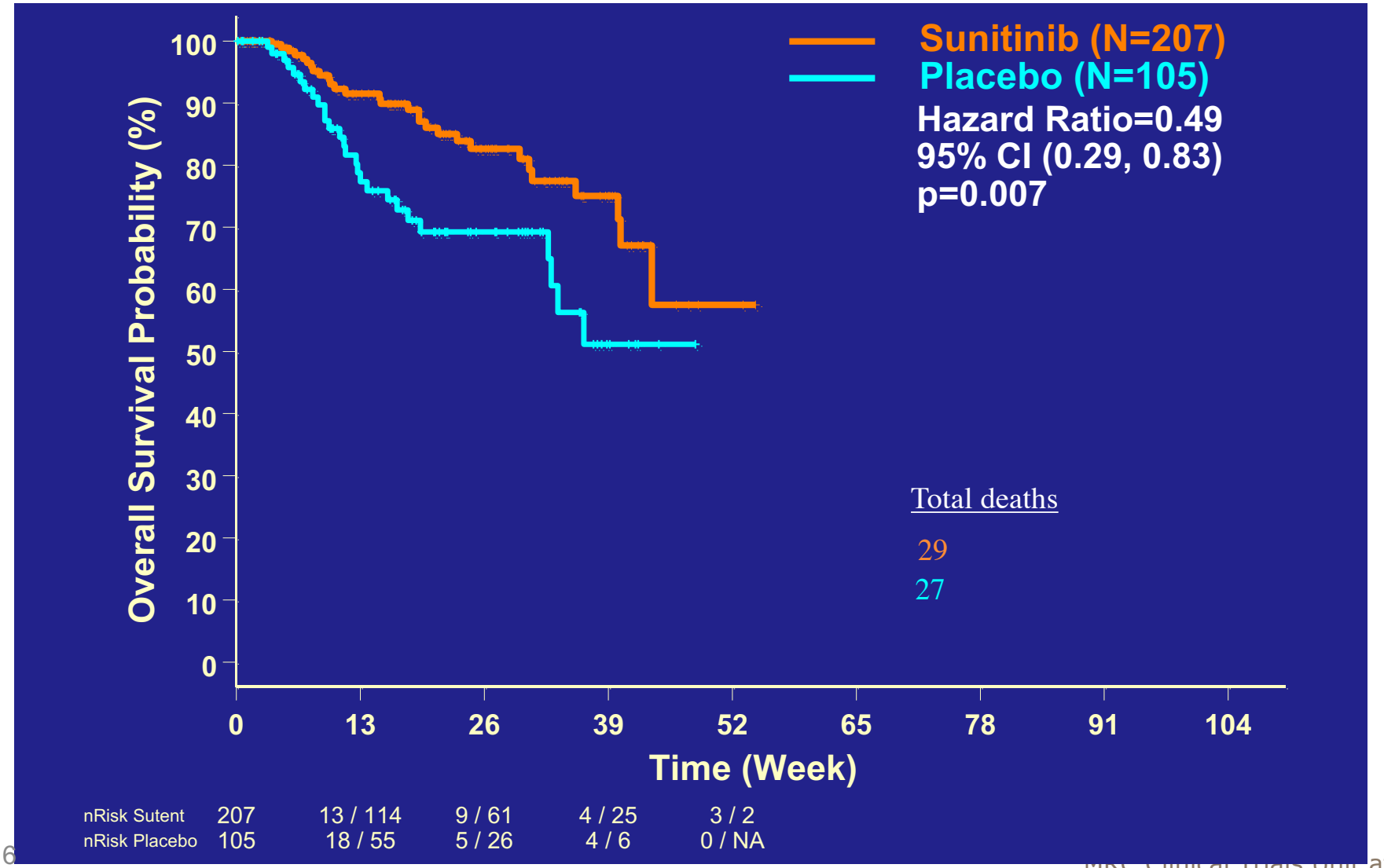
- RCT evaluating sunitinib for patients with advanced gastrointestinal stromal tumour after failure of imatinib
  - Demetri et al, Lancet 2006
- Interim analysis found big treatment effect on progression-free survival
- All patients were then allowed to switch to open-label sunitinib
- Next slides are from Xin Huang (Pfizer)

Time to Tumor Progression
(Interim Analysis Based on IRC, 2005)



with thanks to Xin Huang (Pfizer)

Overall Survival (NDA, 2005)



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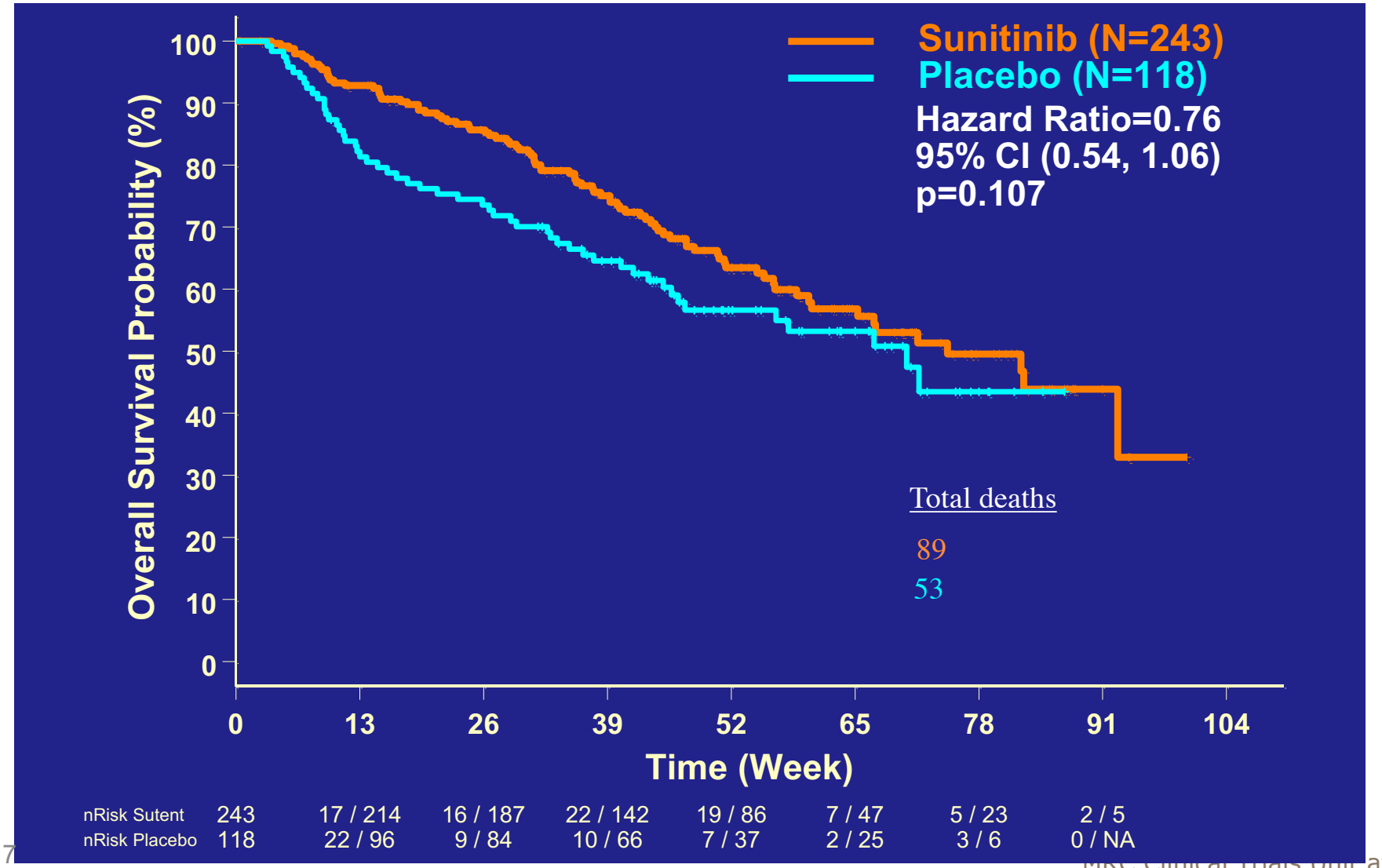
Overall Survival (ASCO, 2006)



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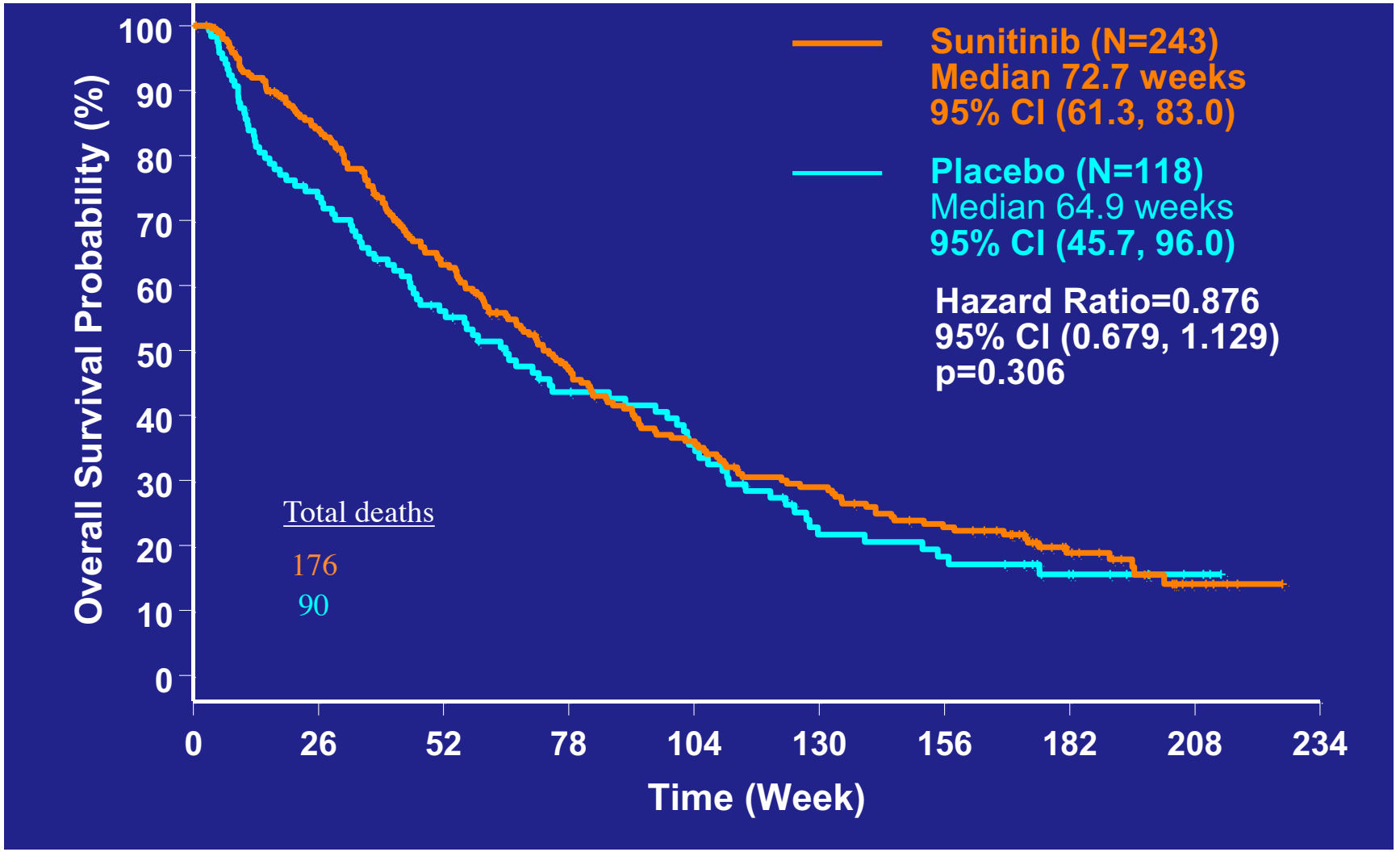
Overall Survival (Final, 2008)



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Sunintinib trial: explanation?

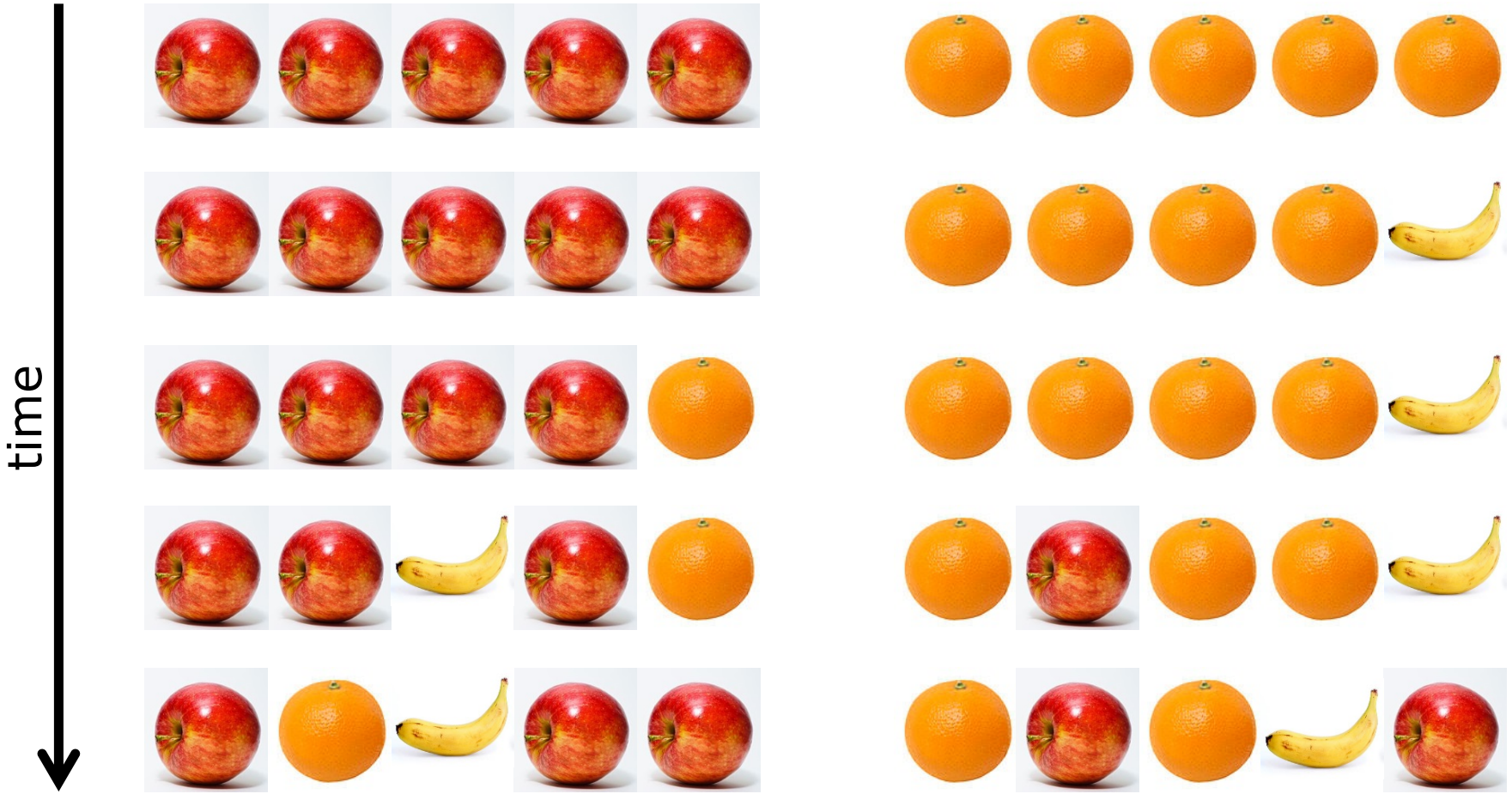
- The decay of the treatment effect is probably due to treatment switching
- Of 118 patients randomized to placebo arm:
  - 103 patients switched to sunitinib treatment
    - 83 switched within 3 months
    - 19 switched before disease progression
    - 4 never treated with placebo
  - 15 patients did not switch
- Questions
  - what was the effect of assignment to sunitinib?
  - what would this effect have been if no-one in the placebo arm had received sunitinib?
    - especially relevant to NICE (National Institute for Health and Care Excellence) evaluations

The plan

What actually happened (1)

What actually happened (2)

What actually happened (3)



Part of a wider problem

- Note on terminology: people often talk about "treatment cross-overs"
  - to avoid confusion with cross-over trials, I use "treatment switches"


- Many trials have not just treatment switching (i.e. to the treatment allocated to the other trial arm), but also more general departures from randomised treatment:
  - changes to non-trial treatments
  - changes to no treatment
  - multiple treatments
  - dose adjustment
  - non-compliance with prescribed treatment


In summary, we are talking about

- Treatment changes in cancer trials
- Nature:
  - switches to other trial treatment
  - changes to non-trial or no treatment
  - etc.
- Reason: clinician decision or patient decision
- Mechanism: typically non-random (patients who change treatment differ systematically from those who don't change treatment)

Plan

1. Treatment changes
2. **Estimands**
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Defining the question

- For sunitinib, the main question of interest (to funders) was
  - "drug now": treatment as actually given in the sunitinib arm (given until clinical decision to stop, usually due to adverse event / progression)

  vs.
  - "no drug": no drug at all, even after progression, because it hasn't been approved
- Instead the trial answered
  - "drug now": as actually given in sunitinib arm
  - vs. "deferred drug": as actually given in placebo arm
- That is, the RCT didn't address the main question
- This is a common, but not universal, setting

Three common questions

- What is the effect of assignment to treatment A *in the circumstances of the trial*? (effectiveness; de facto)
  - could be: A immediately vs. A on progression
- What will be the effect of assignment to treatment A *in other circumstances*? ("alternative effectiveness"?)
  - sunitinib example: NICE's question was sunitinib immediately (with discontinuations as in clinical practice) vs. no sunitinib
- What is the effect of treatment A *per se* (efficacy; de jure)?
  - i.e. while actually given

The three effects estimated here are examples of an estimand = **the thing we want to estimate**

Current thinking in the pharmaceutical world

- The International Committee on Harmonisation (ICH) has a working group on estimands
- They recently (30 Aug 2017) published a draft guidance document:
  - "ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials"
  - consultation period to 28th Feb 2018
- I'm going to outline its proposals
  - very important for pharma trials
  - will affect academic trials

Key message: let the estimand come first

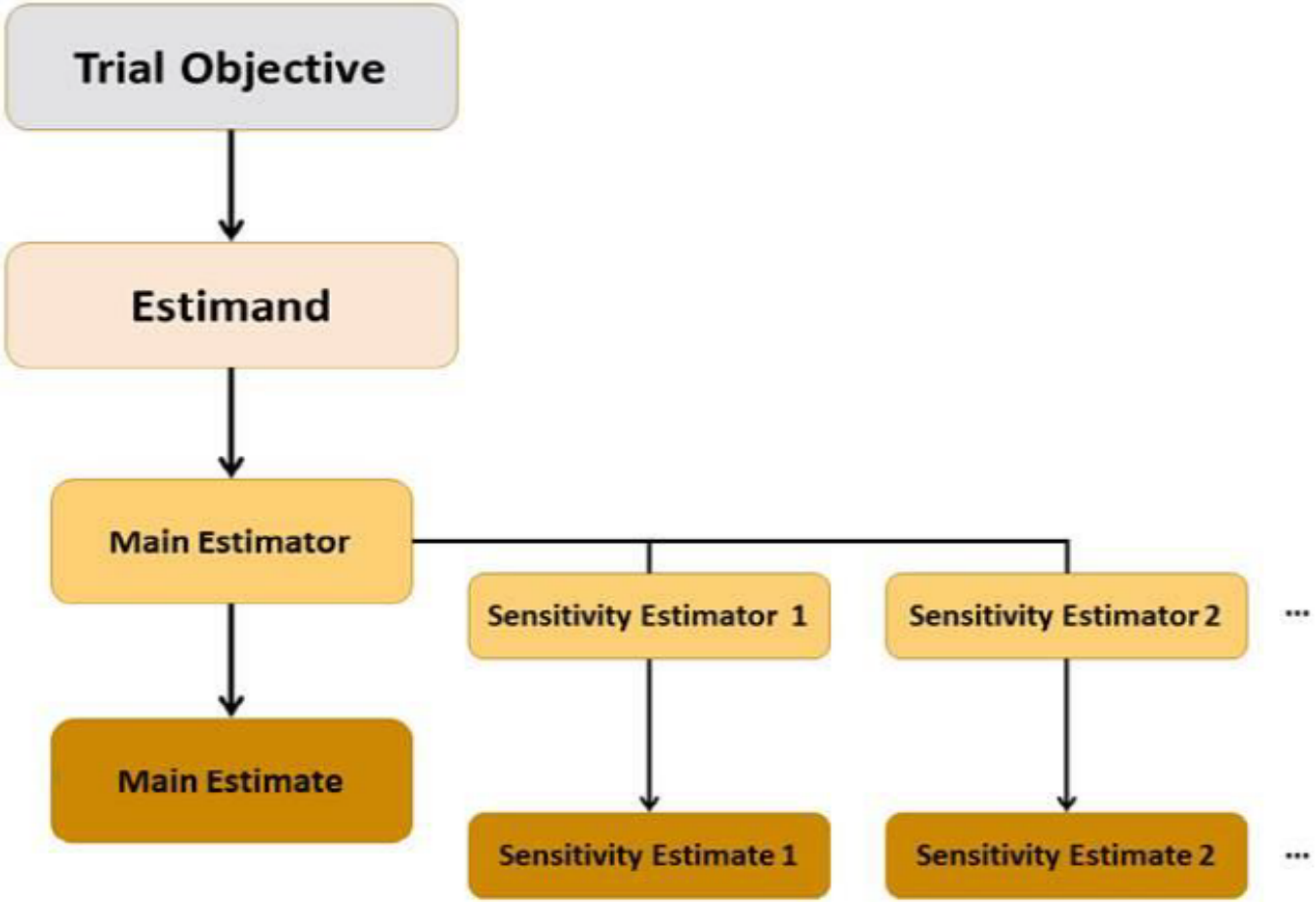

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

"Intercurrent events"

- Intercurrent events are "events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation". E.g.
  - withdrawal from follow-up
  - death [when not a major trial outcome]
  - discontinuation of trial treatment
  - treatment switching [i.e. to other trial treatment]
  - use of an alternative treatment [e.g. rescue]
- Main challenge in defining an estimand is in defining how intercurrent events will be handled

Five strategies for addressing intercurrent events in defining an estimand

1. Treatment policy strategy
   - ignore intercurrent events: we are interested in the effect of assignment to a treatment
2. Composite strategy
   - combine intercurrent events with clinical outcome
3. Hypothetical strategy
   - imagine what would happen if no intercurrent events occurred
4. Principal Stratum strategy
   - restrict to a subgroup who would not experience intercurrent events (however they were randomised)
5. "While on treatment" strategy
   - dangerously vague in my view

Next I'll relate these to analyses.

Plan

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Analysis: toolkit

Method	**Estimand**	**Challenges**
1. Ignore intercurrent events – this is intention-to-treat analysis	Treatment policy	Need to handle missing data
2. Combine	Composite	Interpretation
3. Exclude – censor patients at intercurrent event – IPCW (soon)	Hypothetical	Risk of selection bias
4. Model – model effect of intercurrent events – IV / RPSFTM (next)	Hypothetical / principal stratum	Modelling many treatment effects

IV: idea

- Modelling approach: relate observed outcomes Y to *potential outcomes in the absence of treatment* $Y(0)$ through a "structural model" involving treatment d and a parameter ψ
  - e.g. for continuous outcome $Y(d) = Y(0) + \psi d$
  - for survival outcome we use the RPSFTM (next)
- NB because we must estimate ψ, IV methods are best suited to treatment switches (to other trial treatment)
  - e.g. not for rescue treatments
- Targets the hypothetical estimand e.g. $E[Y(1) - Y(0)]$
  - though Angrist, Imbens & Rubin (1996) showed in the case of 0/1 treatment that the target is better described as a principal stratum estimand

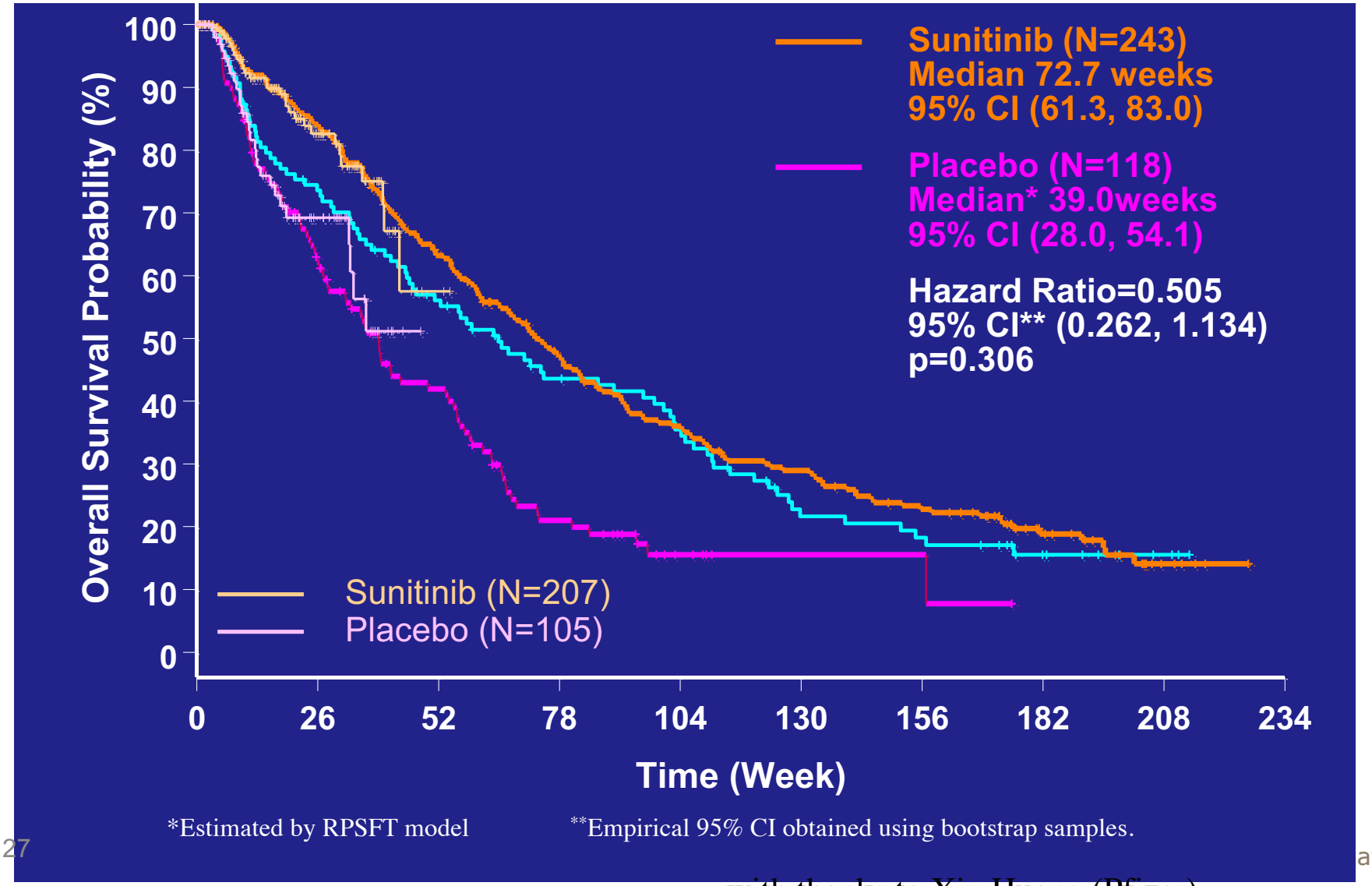
Rank-preserving structural failure time model (brief outline)

- Outcome: T_i = observed lifetime for individual i
- The RPSFTM relates T_i to the same individual's *potential lifetime in the absence of treatment* $T_i(0)$ through a treatment effect ψ (Robins & Tsiatis 1991)
  - T_i^{off}, T_i^{on} = follow-up times off and on treatment
  - treatment increases the T_i^{on} part
  - model: $T_i(0) = T_i^{off} + \exp(\psi) \times T_i^{on}$

good treatment: $\exp(\psi) < 1$

- Interpretation: you have an assigned lifetime $T_i(0)$ which you use up $\exp(\psi)$ ("acceleration factor") times faster when you are on treatment
- Estimate ψ using the fact that $T_i(0)$ is balanced across randomised groups
- Finally compare the T_i in treated arm with the $T_i(0)$ in control arm (White et al, Stat Med 1999)

Sunitinib overall survival with RPSFTM



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IPCW: idea (1)

- Inverse-Probability-of-[not]-Censoring Weighting
- "Exclude" approach: censor at treatment change
- But treatment changes occur to a selected group: e.g. treatment switches are common on disease progression
- We allow for this by weighting
  - weight by inverse probability of remaining on intended treatment, given history
  - requires time-updated covariates, e.g. whether progressed
  - modelling exercise to predict departing from intended treatment given time-updated covariates
  - requires departing from intended treatment to be uncertain

IPCW: idea (2)

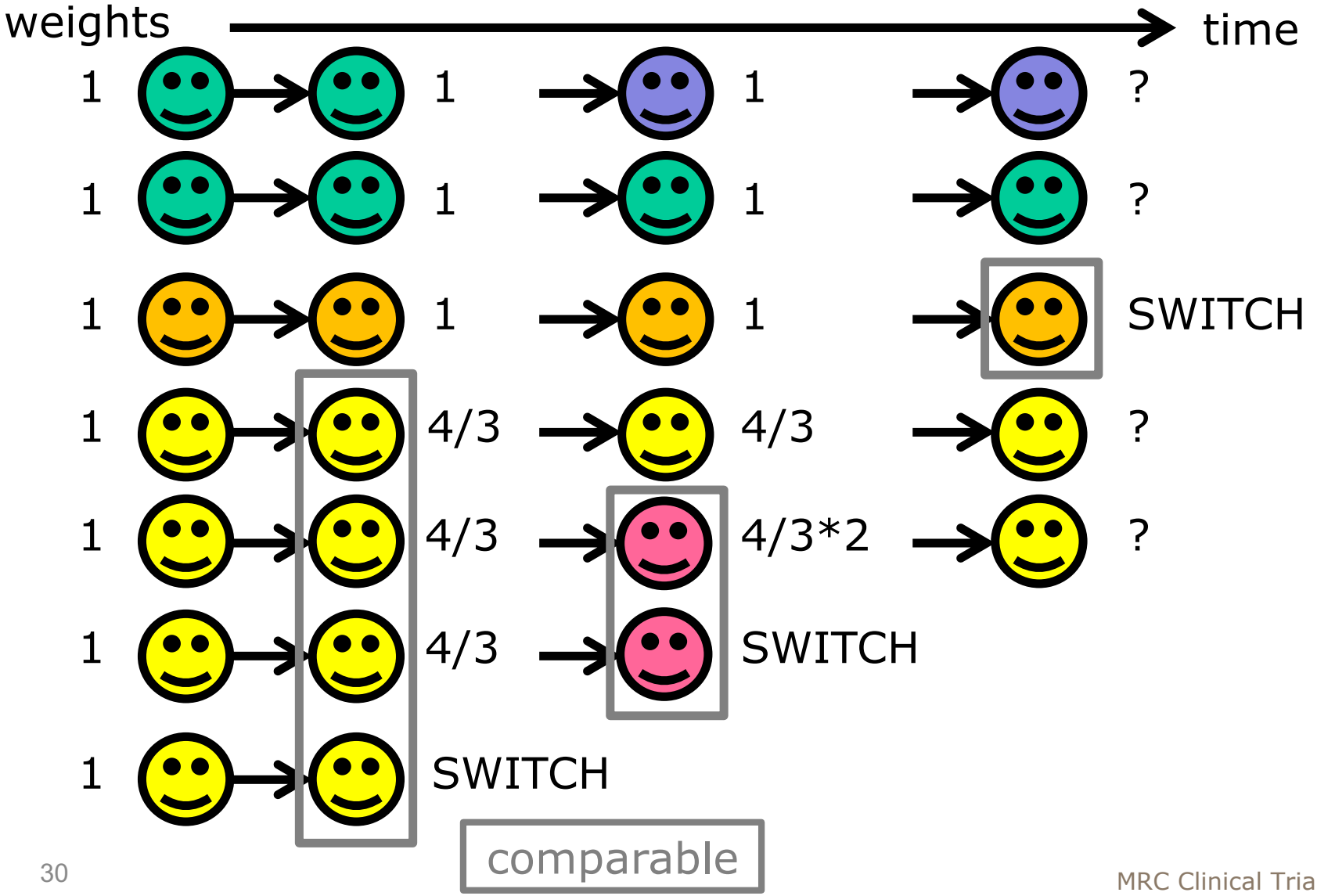
- Underlying assumption: no unmeasured confounders
- We use

  the participants who remain on intended treatment

  to represent

  the potential outcomes of participants who changed treatment, *if they had remained on intended treatment*
- Hence we are estimating a "hypothetical" estimand
  - effect if no-one changed treatment
- NB can handle all sorts of treatment changes

IPCW illustrated: control arm



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Design aspects

- Choose estimand at start of design process
  - or estimands
- If possible, minimise extent of treatment changes
- Choose suitable analysis
- Collect suitable data

Design aspects

Estimand	Analysis	Design requirement
Treatment policy	ITT	Define and record treatment changes (for description & imputation)
		Follow up regardless of treatment changes
Hypothetical	IPCW	No need to follow up after treatment changes
		Collect time-varying covariates that predict treatment changes and outcome
Hypothetical	IV	Define and record treatment changes (for analysis)
		Follow up regardless of treatment changes

More radical ideas

- Do we need to allow the control arm to start experimental treatment at progression?
  - if ultimately the experimental treatment is not funded because of uncertainty about its impact on overall survival, then we have stopped collecting data too soon
- I think there is an argument for a 2nd randomisation (start experimental treatment *vs.* continue control) in the control arm at progression
  - gains extra information about treatment effect
  - makes IPCW assumptions valid

Summary

- Treatment changes take many forms
- Some matter, some don't
- Need to be clear what question we are asking – what is our estimand
- Need to design trial suitably for our estimand
- Need to analyse trial suitably for our estimand

Good recent reference: Hernán MA, Robins JM (2017) Per-Protocol Analyses of Pragmatic Trials. *NEJM* 377: 1391–1398.