Are AD Trial Protocols fit for purpose? -and why are screen failures occurring?

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Conflicts of interest

- None!
- Except VERY interested in ensuring trials are fit for purpose
- And feel conflicted when suitable patients are “thrown out”

Recent scenario

- Mrs VF
- Age 78
- 3 year history of progressive cognitive decline
- Functionally independent
- No significant comorbidities
- On a PPI and a statin only
- MoCA 23
  - STM 2/5
- Already had amyloid PET: positive
- Screened for GRADUATE (gantenerumab, mAb against amyloid, mild AD- prodromal or dementia)
- Free Recall on FCSRT 32
  - Needed to be 27 or below for eligibility
- Known amyloid positive (AD) and now not eligible for trial
- No protocol-specified follow-up for screen fails

Why is this frustrating?

- Cognitively and functionally identical to many who were successfully screened for this trial
- Seems everything relies on a single test on a single day
- No “consolation prize”
- Great deal of investment leads up to the screening
  - identification as potentially suitable
  - further prescreening
  - sending out PCIFs and discussing trial over phone
  - lining up investigator, psychologists
  - consenting and screening time on the day
  - in this case, follow-up appointment to debrief (my private patient)
- Patient hears almost weekly media about latest dementia “breakthrough”

GRADUATE SCREENING- our site

- 68 screened
  - Most extensively assessed and prescreened
    - All checked for top level exclusions before screening
  - All diagnosed with AD by a specialist
  - Many with known positive amyloid PET
- 34 screen fails
  - 8 MMSE below 22
  - 17 FCSRT cueing index above 0.67 or free recall above 27
  - 9 other
    - PHx CVA
    - Found to be on anticoagulant
    - Abnormal LFTs
    - Low B12/high homocysteine
    - Amyloid negative (one only- positive for NAV Amyloid PET)
  - 3 successfully rescreened= 37 randomized
- Only one of 35 who got as far as amyloid PET was amyloid negative
  - And was positive on the more accurate NAV amyloid tracer
  - Shows all who **screen failed** were well characterized and were “trial suitable”
    - Failed to be in “Goldilocks zone” cognitively on the day
    - Did not fail as did not have otherwise suitable Alzheimer’s

CLARITY SCREENING- our site

- Also a mAb (lecanemab/ BAN 2401)
- 32 screened
- 20 screen failed
  - 8 MMSE below 22
  - 6 WMS (Weschler Memory Score) LMII too high
  - 6 other
    - Only one who proceeded that far had negative amyloid PET
      - again, showing almost all those who screen failed were trial suitable

Screen failures- issues

- Near misses on MMSE or other memory test
  - in all other respects suitable
  - ?performance anxiety on the day
    - or unfamiliar environment
    - many known to recently have scored in acceptable range on MMSE then screen fail on it
- Are we selecting a representative sample of those who may ultimately be treated?
  - “super performers” on the day
  - how many in the general population will be in this Goldilocks zone?
  - many don’t even get to screening as comorbidities etc
    - But are likely to be treated if drug marketed
- What of those who just miss out and are in all other respects the same as those who screen successfully?
  - Some of whom know they are amyloid positive

Arguments for strict cognitive selection criteria

- Have to set the boundary somewhere
  - If entirely up to PI, would have a very heterogenous population
  - This may lead to a type 2 error (false negative trial)
- Need to use tests that specifically select for one aspect of "hippocampal" memory uniquely affected by AD
  - ie rapid forgetting not assisted by cueing
- Trial needs a high MMSE/low memory group
  - High MMSE-more likely to last the distance (2+years)
  - Low "hippocampal" memory test result- more likely to deteriorate on placebo

Any evidence that AD therapies in real world being used on patients **unlike** those in trials?

- YES, if initial FDA accelerated approval of aducanumab an indication
  - ANY stage of AD
    - Subsequently restricted to mild AD
  - No need for proof of amyloid
- AND safety issue/s
  - No requirement for regular MRIs
  - No advise on initial dose titration
  - No advise on dose adjustments if ARIA detected
- No advise on duration of therapy
  - Potentially could be continued into severe AD stage

What would a “fit for purpose” trial look like?

- Allow “near misses” in
  - Rescreen
  - Dialogue between PI and sponsor’s medical staff
- Parallel trial for screen fails
  - Later combine results OR only need to submit results of trial of those who screen successfully but use other trial to support submission
    - Safety data
    - “Similar” effects of drug even if not significant
- Certainly need further data (phase IV or another phase III) after approval
  - As BIOGEN are doing
    - But <9years preferable!

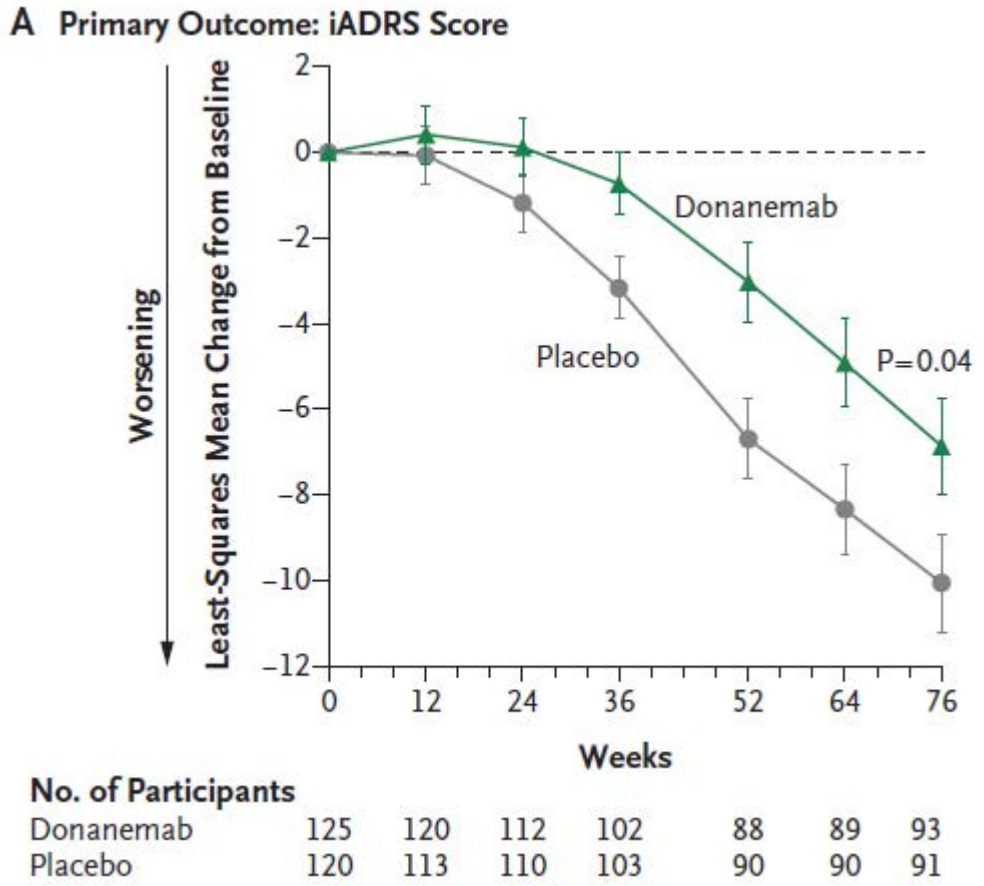
Are newer trial designs more fit for purpose?

- TRAILBLAZER (donanemab)
  - Needed tau PET positive but not too positive
  - Ceased dosing if amyloid PET below pre-set threshold
    - <11 CL on one scan
    - Or >10<25 on 2 consecutive scans
    - 55% achieved this by week 56
- Likely to select a population more likely to benefit and allows dosing to cease when amyloid removed
  - Estimated it would take 14+ years for amyloid to rise again to 90CL
- But are we really going to do both amyloid and tau PETs at baseline and serial amyloid PETs to monitor response?

Donanemab (N3pG, Lilly)

- Rapid lowering of Aβ load by 24 weeks; those normalized to 11CL did not show return at 76 weeks; 14 years to get back to 90CL
- Significant relationship of Aβ lowering and slowing of clinical decline (28% overall, 42% APOE4+)
- Dramatic lowering of plasma p-tau217 even as early as 12 weeks
- Major reductions in tau-PET in fronto-parietal regions; lowest starting tau-PET had best clinical benefit.

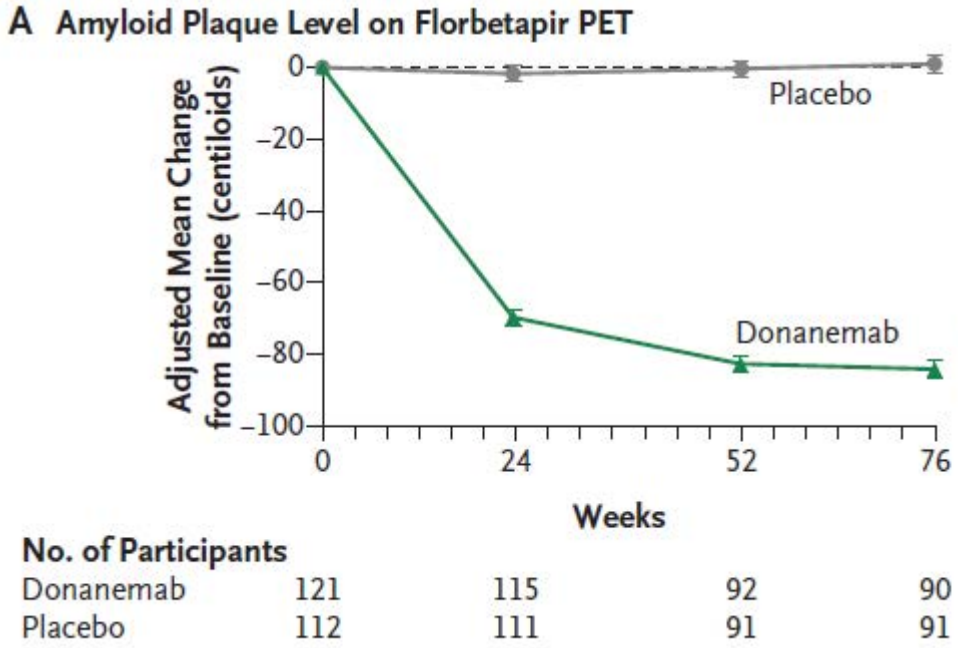
Donanemab (Trailblazer-Alz PhII)
Primary Outcome (iARDS=ADAS-Cog13 + ADCS-iADL)



	Difference in Least-Squares Mean Change	
	Donanemab vs. placebo	95% CI
	points	
Wk 36	2.44±0.96	0.55–4.33
Wk 52	3.67±1.26	1.19–6.15
Wk 64	3.42±1.42	0.63–6.21
Wk 76	3.20±1.56	0.12–6.27

Prodromal/mild AD; Intermediate flortaucipir PET 1.11-1.46.
23-39% slowing. Mintun et al., NEJM 2021

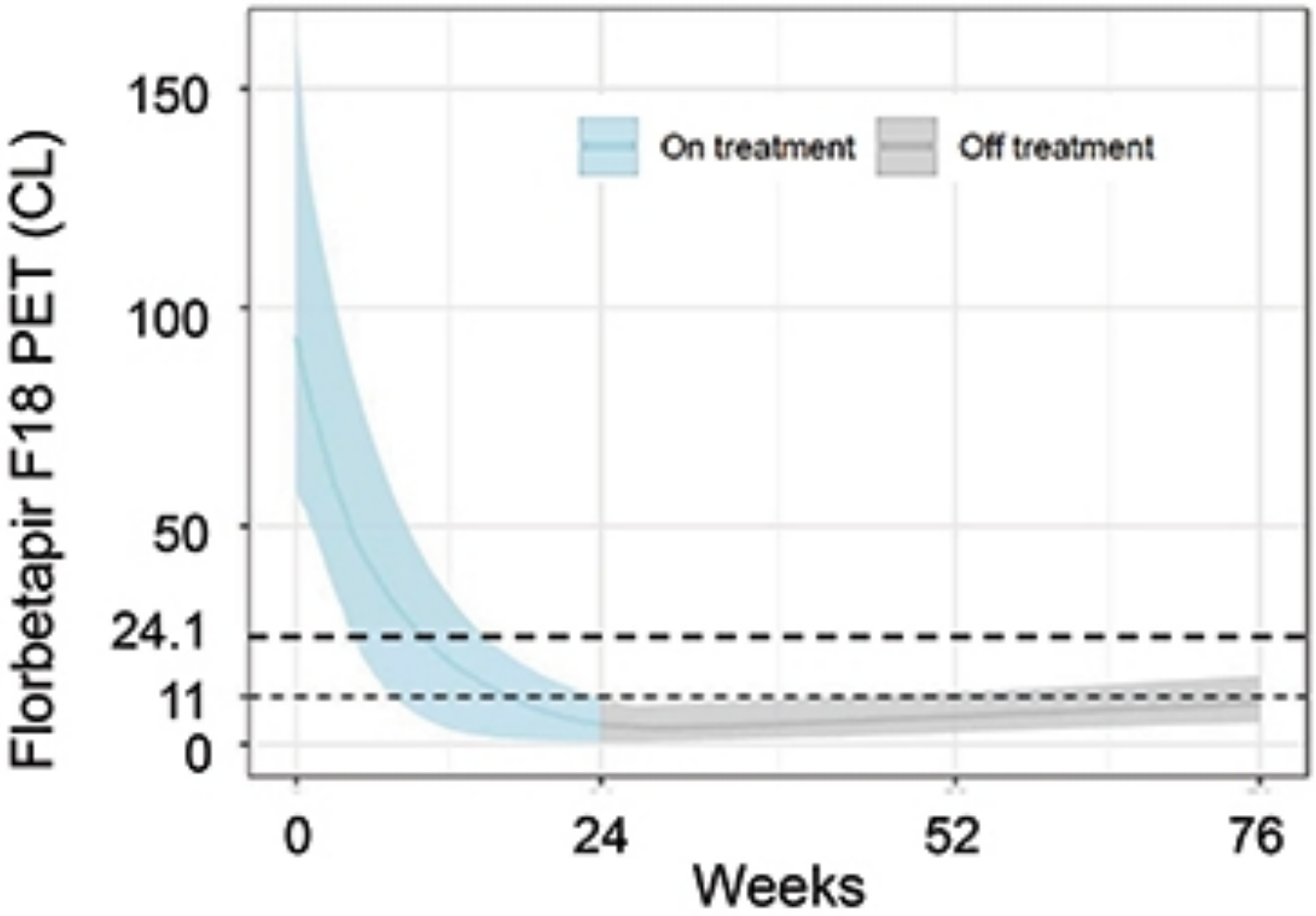
Donanemab (Trailblazer-Alz PhII)
Secondary Outcome Aβ-PET (Florbetapir)



	Difference in Adjusted Mean Change		Amyloid-Negative Status, Donanemab
	Donanemab vs. placebo	95% CI	
	centiloids		*no. (%)*
Wk 24	−67.83±3.16	−74.04 to −61.61	46 (40.0)
Wk 52	−82.30±3.41	−89.02 to −75.59	55 (59.8)
Wk 76	−85.06±3.87	−92.68 to −77.43	61 (67.8)

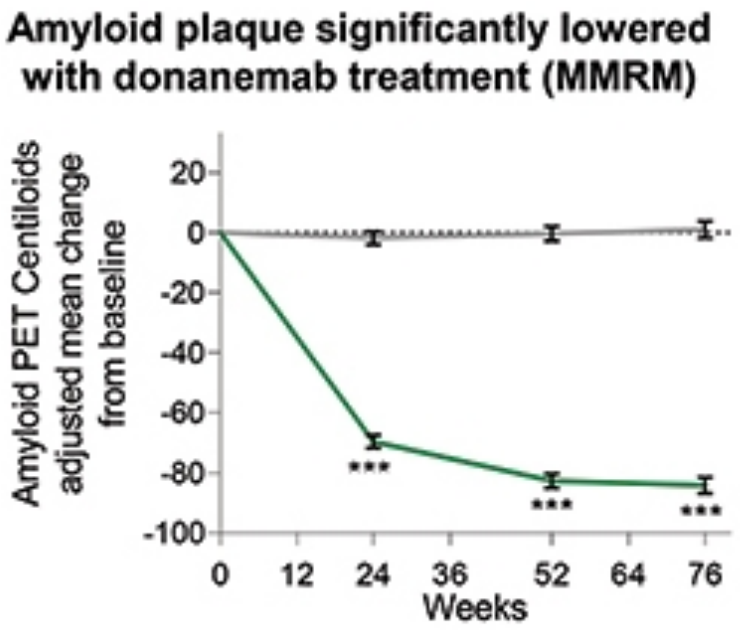
85% CL reduction, most within 24 weeks
68% negative baseline at 76 weeks.
Mintun et al., NEJM, 2021

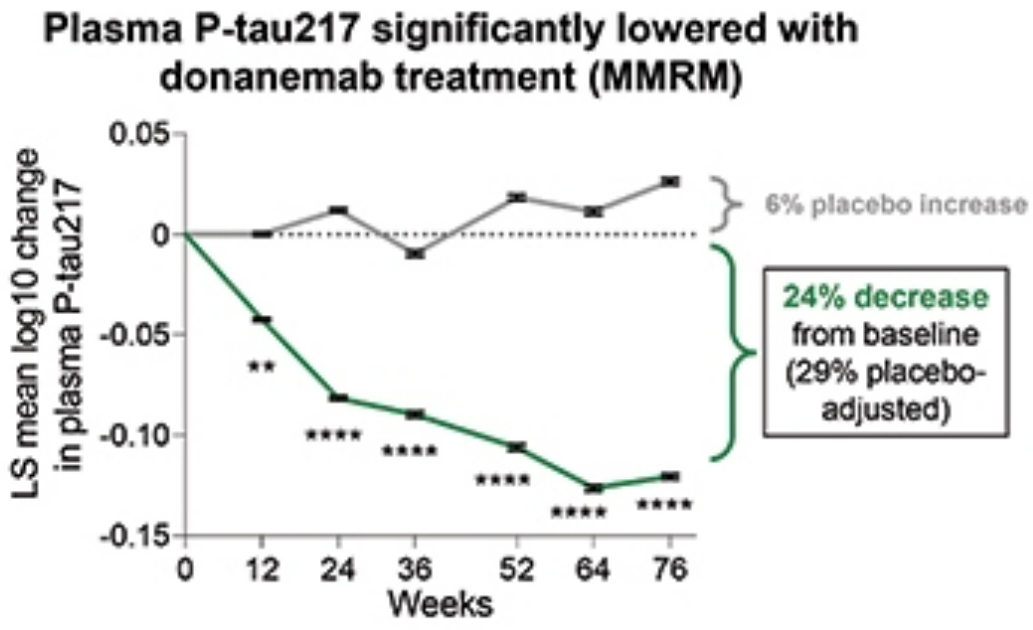
Donanemab (Lilly): subjects whose Aβ load fell below 11CL at 24 weeks, stayed negative at 76 weeks;
estimate 14 years to return to starting levels (90CL)



Lilly AAIC, 2021

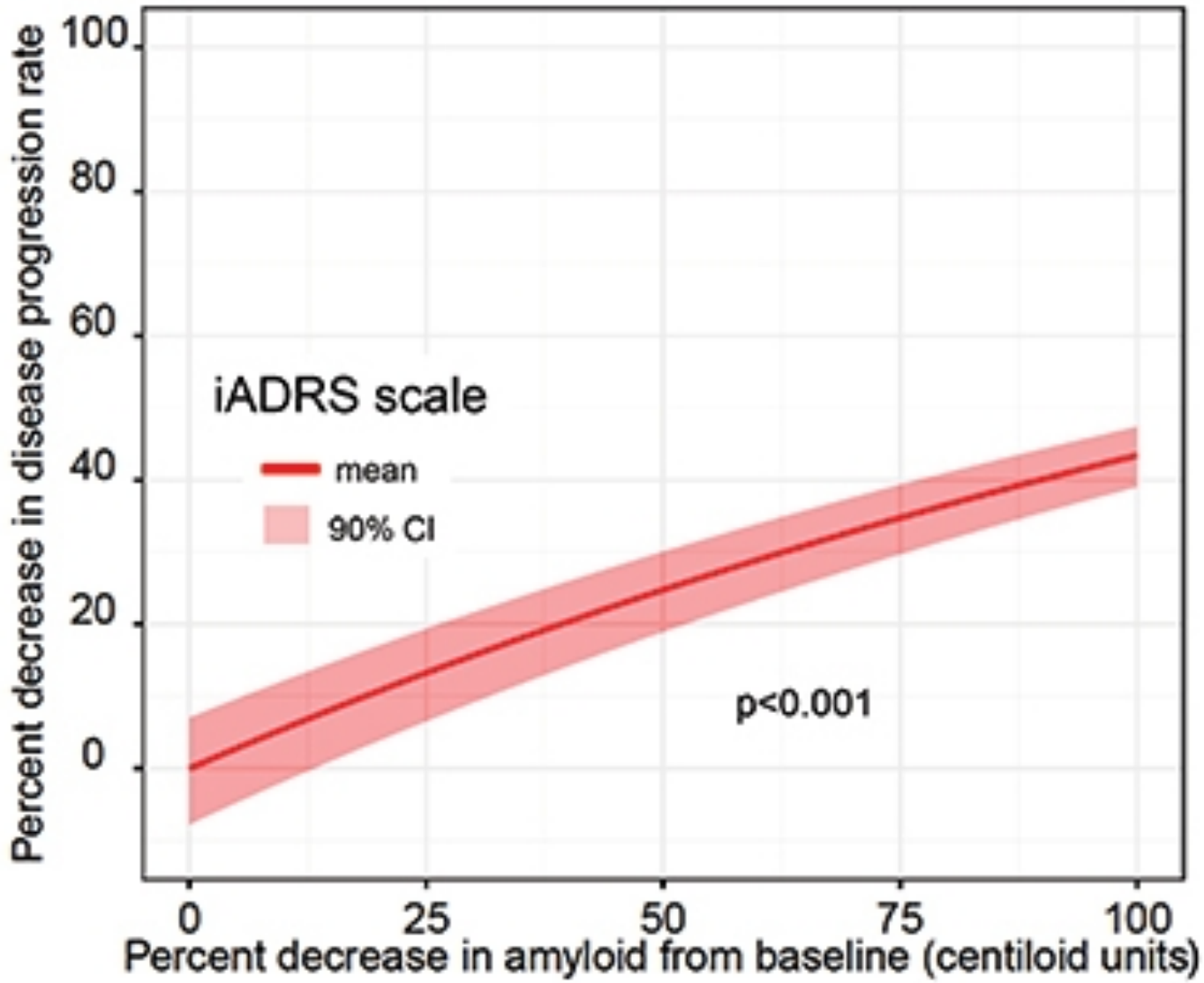
Donanemab: concomitant Aβ load and plasma p-tau217 lowering





Lilly, AAIC, 2021

Donanemab: modeled data significant relationships between Aβ lowering and slowing of cognitive decline; 28% slowing overall, 42% slowing in APOE4 carriers



Lilly, AAIC 2021

Conclusions

- Likely that current inclusion/exclusion criteria exclude patients who would respond to IP the same as those successfully screened
- Likely that approved drugs will be used on many who would screen fail pivotal Phase III protocols
- Negative impact on those who screen fail: need SOP for follow-up
- But maybe current selection criteria are a necessary “evil”
- Newer trial designs may better reflect how drugs may be used if marketed
- Need marketed drugs to only be approved for a population similar to those in the pivotal trial
- And need safety monitoring/action advise based on that used in the trials