Sputum biomarkers and regulatory innovation for MDR-TB regimens

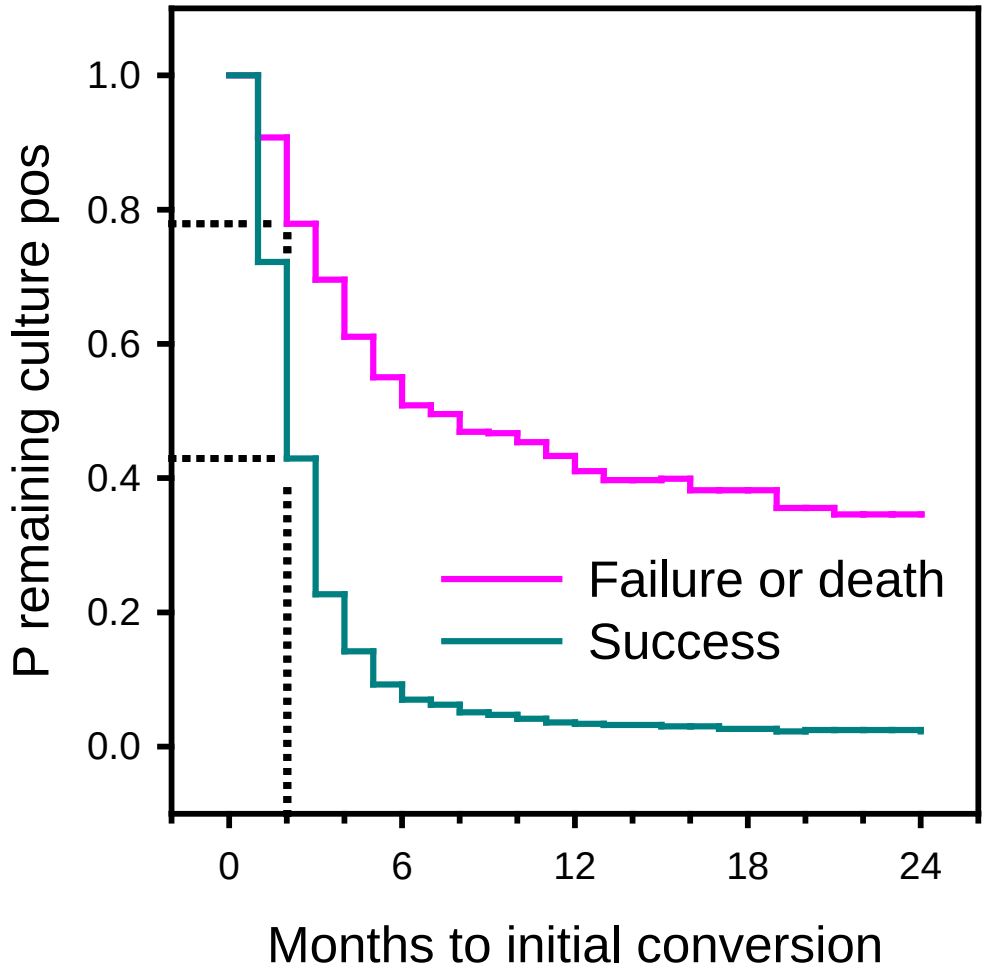
RS Wallis, MD, FIDSA, FRCPE
Chief Science Officer, Aurum Institute, Johannesburg
rwallis@auruminstitute.org

EMA TB workshop
26 Nov 2016, London

THE AURUM INSTITUTE

M2 culture as a predictor of treatment success

- A 2015 analysis of 2 cohorts of 1712 MDR-TB patients found conversion to negative at 2 months using solid culture medium was strongly associated with success *vs* failure or death (OR=3.6 overall, 4.1 in HIV-negative patients).
- The PPV of M2 conversion for cure in the study dataset was 92%.
- New regimens with superior conversion at M2 therefore are highly likely to show superior success rates.

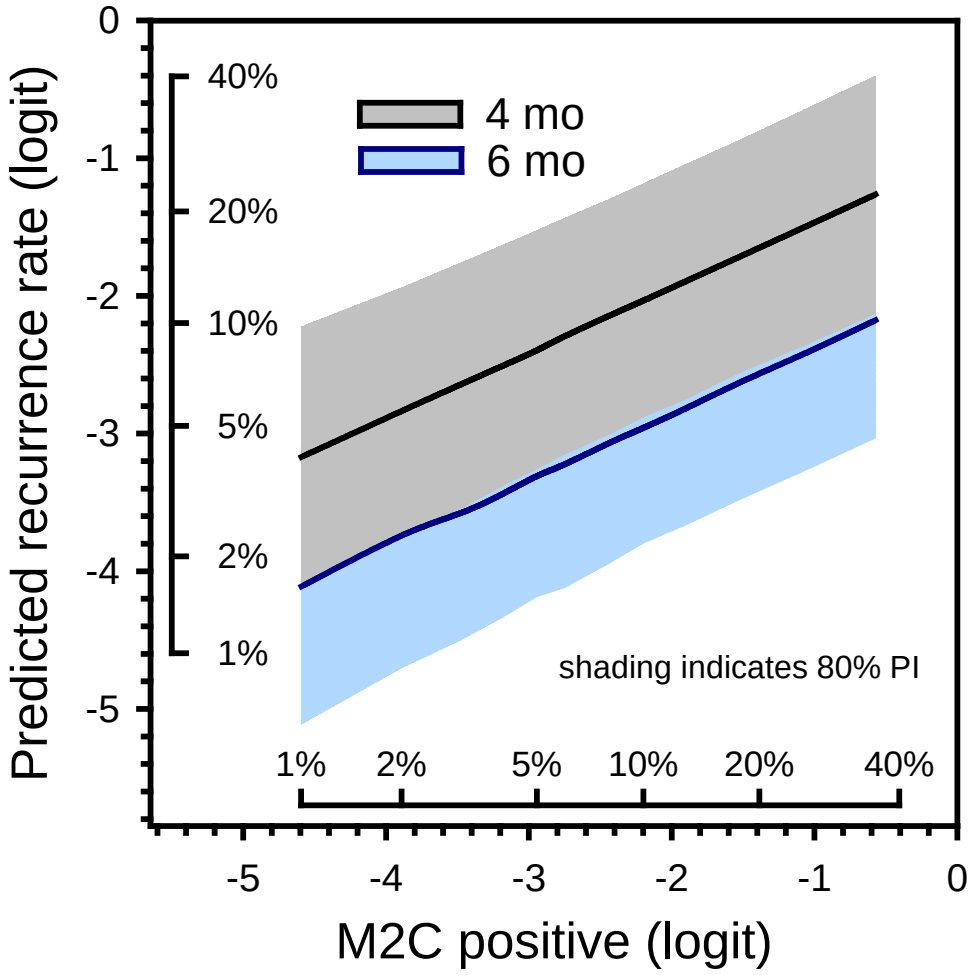


Kurbatova, ***Lancet RM*** 2015

THE AURUM INSTITUTE

M2 culture and duration as predictors of relapse

- A 2013 analysis of 24 trials published from 1973 to 1997 of 58 regimens studied in 7793 patients identified positive month 2 culture status using solid medium (M2C) and treatment duration as independent predictors of relapse.
- Predictions took the form: logit(relapse) = a+b*x*+c*y*, where *x*=logit(M2C) and *y*=log(duration)

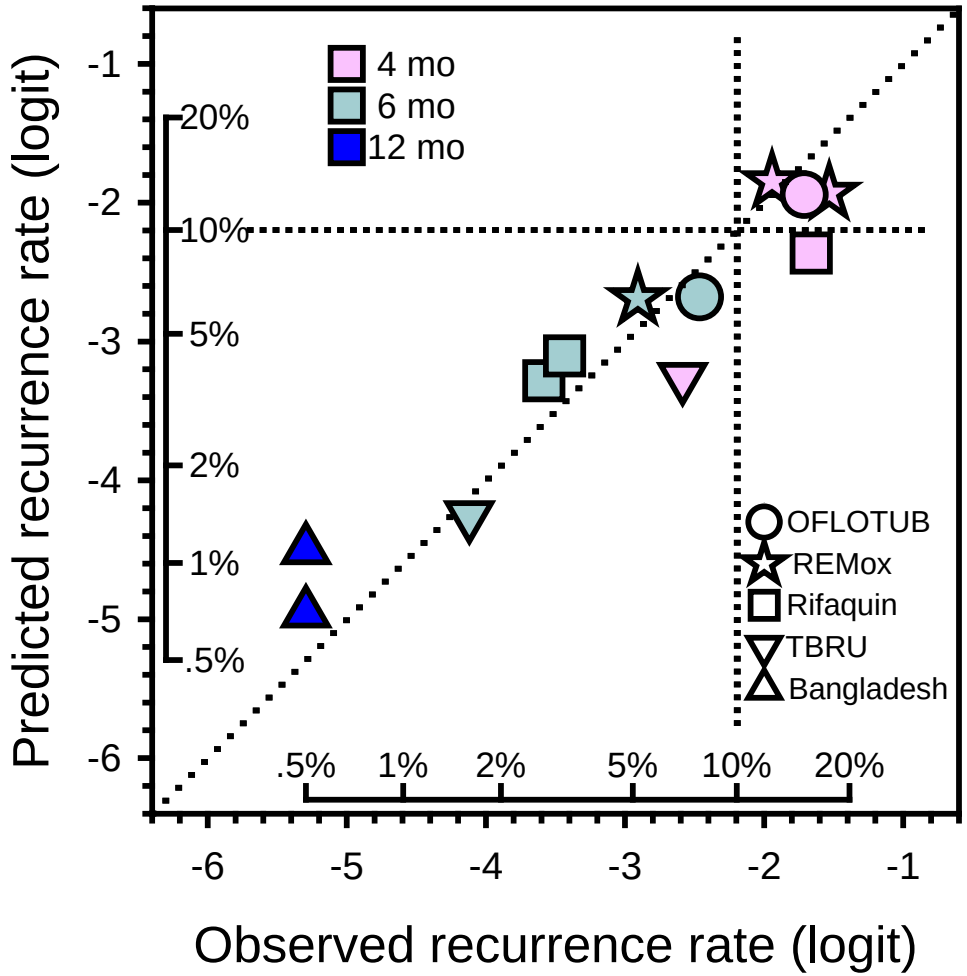


Wallis, ***PLoS One*** 2013

THE AURUM INSTITUTE

M2 culture and duration as predictors of relapse

- The model was subsequently validated using independent data from 6 studies of 12 regimens involving 3907 patients. Predicted and observed relapses correlated at 0.94.
- The model was robust and generalizable, as FQ trials were predicted without prior FQ data, the TBRU treatment shortening trial was predicted without prior host data, and the Bangladesh regimen trials were predicted without prior MDR or clofazimine data.

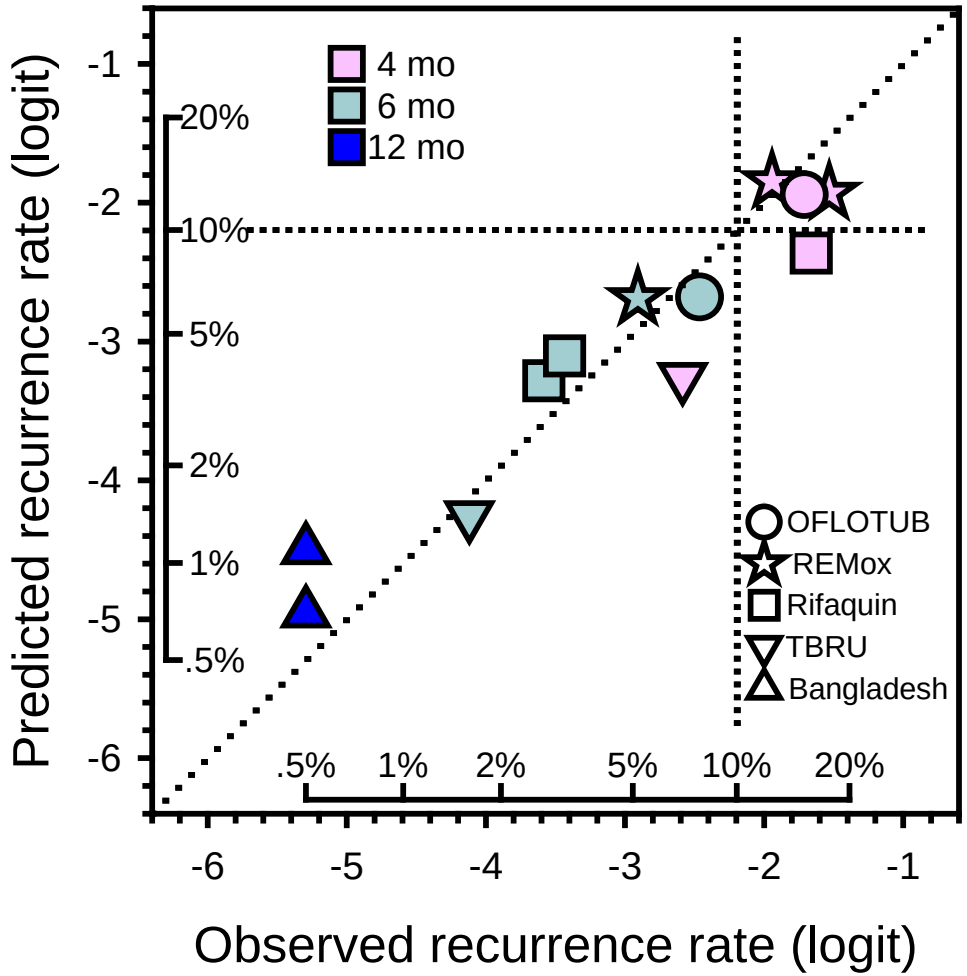


Wallis, ***PLoS One*** 2015

THE AURUM INSTITUTE

M2 culture and duration as predictors of relapse

- **TBRU treatment shortening trial**: 390 HIV-negative patients with non-cavitary disease at baseline and negative cultures at M2 were randomly assigned to 4 or 6 months total treatment. The study succeeded in showing low relapse rates overall (7.0% and 1.6%, respectively), but failed by finding that duration was a predictor of relapse even in this low risk population.

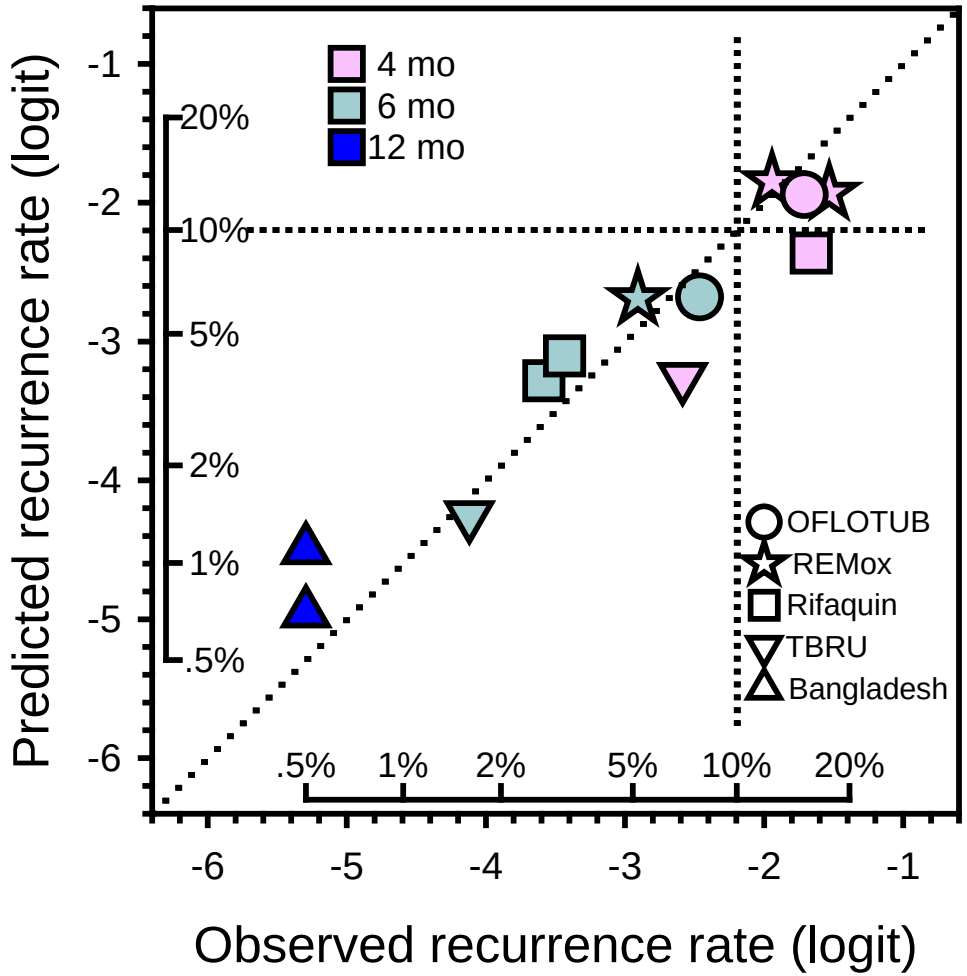


Wallis, ***PLoS One*** 2015

THE AURUM INSTITUTE

M2 culture and duration as predictors of relapse

- **Bangladesh regimen studies**: MDR-TB patients were enrolled into 2 open label single arm cohort studies of a 12-month clofazimine-containing regimen in Niger and Cameroon. 149 cured patients were followed for >1 year post cure. M2C positive proportions were 6% and 13%. No relapses were detected.



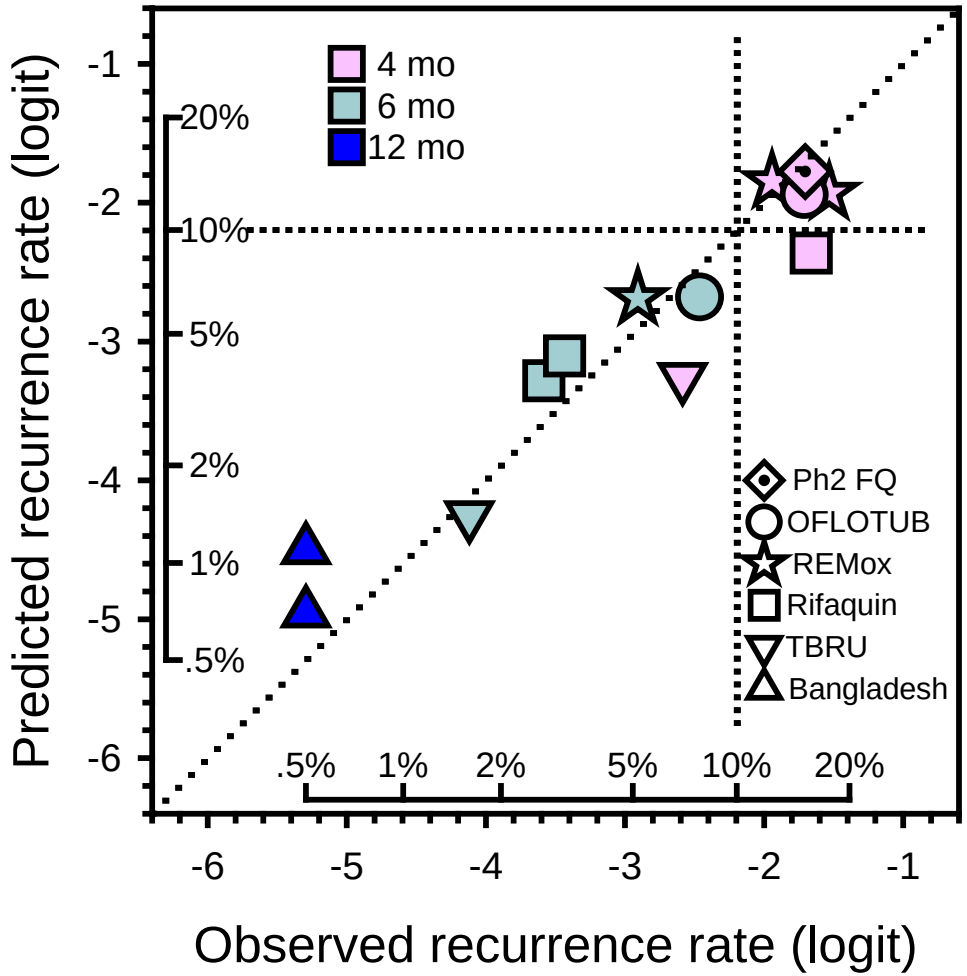
Wallis, ***PLoS One*** 2015

THE AURUM INSTITUTE

M2 culture and duration as predictors of relapse

- We also found that the weighted mean results of all four 4-month FQ arms in OFLOTUB, REMox and Rifaquin could be predicted based on phase 2 data from 5 trials of 6 FQ regimens involving 443 patients.
- Database now includes 30 studies, 70 regimens, and 11700 patients.
- M2C is the sole TB treatment biomarker meeting the criteria of Chau *et al* for "known valid".

Clin Cancer Res 2008



Wallis, ***PLoS One*** 2015

THE AURUM INSTITUTE

Innovation to combat drug-resistant infections

- 25 years ago, the creation of new regulatory approval mechanisms (conditional authorization and accelerated approval) relieved ethically unacceptable bottlenecks in HIV ARV drug development.
  - They permitted the substitution of a biomarker for a clinical endpoint, thus expediting new treatments for serious or life-threatening diseases based on phase 2 data, but did not eliminate the requirement to conduct phase 3 trials.
- We now face a similar crisis for drug-resistant bacterial infections.
  - 2 innovative mechanisms (Adaptive Pathways and Special Medical Use) promise expedited approvals restricted to patients with high unmet need and few treatment alternatives, based on limited clinical data. Approvals are tied to a requirement to report outcomes, but not to phase 3 trials. Approvals may expand to additional populations as additional safety and efficacy data are gathered.

Innovation to combat drug-resistant infections

Avycaz
ceftazidime and avibactam
for injection (2.5 g)

Approved by FDA in 2015 for complicated intra-abdominal and urinary infections based on 2 ph2 trials, each with 100 Avycaz-treated patients.

"As only limited clinical safety and efficacy data are available, reserve Avycaz for use in patients who have limited or no alternative treatment options"

CRESEMBA®
(isavuconazonium sulfate)
372 mg for injection · 186 mg capsules

Approved by FDA in 2015 for mucormycosis based on 1 single arm open label trial with 37 patients and only historical controls. (Marty, ***LID*** 2016)

NOVARTIS
Lamprene

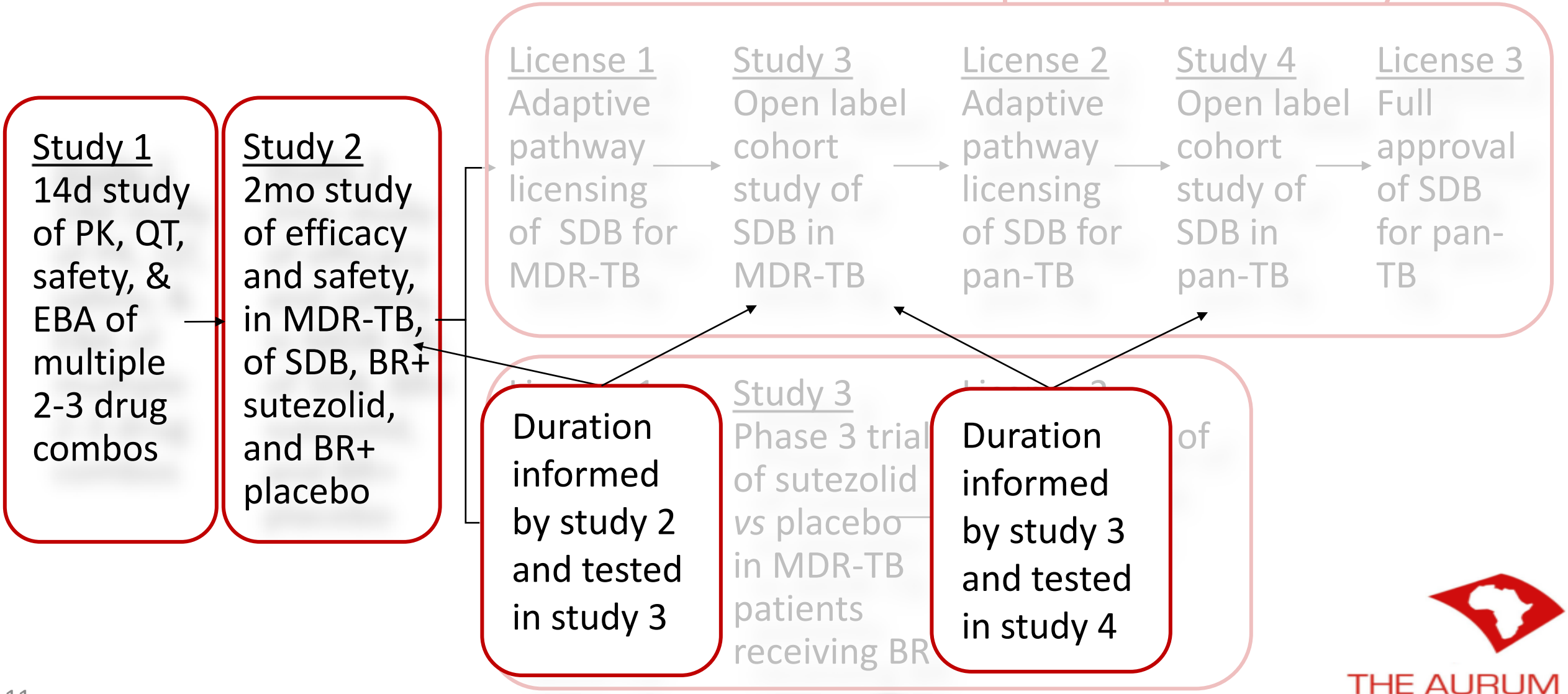
Provisionally recommended by WHO in 2016 as a part of short-course regimens for selected MDR-TB patients despite the complete lack of randomized controlled phase 3 trial data, the absence of regulatory approvals of clofazimine for TB, and some uncertainty as to how patients are to be determined eligible.

THE AURUM INSTITUTE

Sutezolid as a test case for adaptive pathways

- A linezolid analog with superior anti-TB activity in preclinical studies and superior safety in phases 1-2, acquired by Sequella from Pfizer in 2013.
- Sutezolid is a potentially important component of new “pan-TB” regimens comprised entirely of new agents without pre-existing resistance
  - Consistent with the recently published WHO target profile for such regimens, and with the designation as a high priority area for TB research by funders
- Aurum Institute is exploring ways to support development of sutezolid as a part of a new pan-TB regimen with delamanid and bedaquiline (SDB)

Sutezolid as a test case for adaptive pathways



THE AURUM INSTITUTE

MDR-TB as a test case for adaptive pathways

- Major global unmet medical needs would be addressed
  - Creating a new, shorter, more effective TB regimen not requiring DST
  - Shortening by 2-3 years patient access to this regimen
- An existing global infrastructure can be harnessed
  - Dedicated hospitals, trained physicians, mandated prescribing policies
  - Globally accepted mechanisms for outcome reporting
  - Normative roles of multiple international and national bodies
  - Precedented engagement of TB control programs to test new regimens under “real-life” conditions
  - Fully qualified biomarker
- Success in MDR-TB can be readily adapted/expanded to DS-TB

Questions for discussion

- Superior culture conversion formed the basis of the conditional/accelerated authorizations of bedaquiline and delamanid. Is M2C sufficiently validated to advance a novel pan-TB regimen via the adaptive pathway?
- It is generally required that combination treatments justify each component by showing its contribution to the desired outcome. Is the sutezolid+BR arm of study 2 necessary and sufficient for this purpose?
- In adaptive licensing, the benefit-risk balance informs the selection of patient populations and the size of required safety and efficacy databases. Is the progression from MDR-TB to pan-TB appropriate for the adaptive development of an entirely novel regimen? If so, how many subjects need be included in study 2 to proceed with the first adaptive pathway licensing for MDR-TB?

rwallis@auruminstitute.org

THE AURUM INSTITUTE