



Time to Sputum Culture Conversion as a Trial Endpoint: Re-Use and Cross Study Analysis of Standardized Tuberculosis Trial Data

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Abstract

Endpoints in drug trials need to be “well defined and reliable”¹. Whether the “time-to sputum clearance” endpoint in tuberculosis trials predicts symptom resolution is not known so we performed a cross-study analysis to assess this correlating. This project demonstrates the feasibility of performing cross study analyses on legacy research studies converted to the CDISC/HL7 Tuberculosis data standard². The datasets were made publicly available by the Centers for Disease Control and Prevention. Using CDISC derived ADaM data, we performed a time-to sputum culture conversion (time of the first of two consecutive negative sputum cultures for *M. tuberculosis* with no intervening positive cultures) separately for each treatment regimen in the three studies and for the aggregated database. Time-to symptom resolution was similarly analysed for each study and for the aggregated database; symptom resolution at a fixed time point (8th week of intensive treatment) was also described. The time to sputum clearance and time to symptom resolution in patients with drug-sensitive tuberculosis showed parallel resolution over time. Time to sputum culture conversion best correlated with resolution of productive cough OR: 1.54 [1.01, 2.33] compared to cough, fever, weight loss or any combination of the latter symptoms. The surrogate endpoint was used in a recent NDA approval. Data in standard format enables cross study comparisons of efficacy endpoints and can inform trial designs for drug development. We plan a comparison of time to analyses across drug sensitive and drug resistant tuberculosis in a follow up study.

Introduction

A third of the world’s population is infected with tuberculosis (TB); drug development for resistant TB is an urgent public health concern. Compared to drug-sensitive TB, multidrug resistant TB (MDR-TB) treatment is prolonged; and trials challenging to perform. Furthermore, data from TB trials are submitted to the FDA in proprietary, nonstandard formats; data standards that support submissions and their analysis facilitate the development of new treatments for this fatal disease. The research benefits may expand beyond the initial use if data is aggregated across different submissions. Surrogate endpoints do not reflect how a patient feels, functions and survives. Historical studies have shown that eradication of *M. tuberculosis* made patients survive and feel better, but whether they improved with FASTER eradication (time-to analysis) is not known. We describe the review division and the Office of Biostatistics’ exploration of this new endpoint for clinical trials of MDR-TB through re-use of de-identified, legacy converted data of studies conducted by the CDC in drug sensitive TB. The Computational Science Center provided technical support for a legacy data conversion contract (RFTOP - RQ 109022).. The project was intended to reanalyse original trial endpoints and perform explorations of a novel time to sputum culture conversion endpoint and its correlation to resolution of symptoms of tuberculosis in the consolidated converted legacy data.

Methods and Results

Endpoints in Tuberculosis:

We reviewed the study design and endpoints used in the approval of the current TB drugs. These drug approvals relied on the eradication of *Mycobacterium tuberculosis* from the sputum, that is the conversion from a baseline positive sputum culture to negative⁶.

Endpoints Used in Trials of Approved TB Drugs

Approved Drug	Year	Endpoint	Statistics
Ethambutol (Eth)	1967	6m sputum conversion	Descriptive
Rifampin (R)	1971	6m sputum conversion	Descriptive
Rifampin + INH + PZA	1994	6m sputum conversion	Difference; 95% CI
Rifapentine	1998	Relapse	Difference; 95% CI

Legacy datasets:

Data from two studies conducted in drug sensitive tuberculosis was converted and re-analysed by FDA. Study 27 was a randomized, double-blind, Phase II clinical trial assessing the impact of substitution of moxifloxacin for ethambutol, whereas Study 28 was a randomized, double-blind, Phase II clinical trial assessing the impact of substitution of moxifloxacin for isoniazid in standard intensive phase TB treatment regimen on the 2-month sputum culture conversion rate.

Treatment Regimens in Study 27 and 28

Regimen	STUDY 27 Treatment Phase Intensive (8 weeks)	Continuation (18 wks)
Daily control regimen	HRZE daily (+ moxifloxacin placebo)	ATS/IDSA/ CDC- recommended regimen
Daily moxifloxacin regimen	HRZMoxi daily (+ ethambutol placebo)	
Intermittent control regimen	HRZE daily for 2 week, then thrice-weekly (+ moxifloxacin placebo)	
Intermittent moxifloxacin regimen	HRZMoxi daily *for 2 week, then thrice weekly (+ ethambutol placebo)	

Regimen	STUDY 28 Intensive phase (8 weeks)	Continuation (18 weeks †)
Control regimen	HRZE daily (+ moxifloxacin placebo) ‡	ATS/IDSA/ CDC- recommended regimen
Moxifloxacin regimen	HRZMoxi daily (+ ethambutol placebo)	

H – Isoniazid, R – rifampin, Z – pyrazinamide, E – ethambutol, Moxi – moxifloxacin E – ethambutol

Correlation of FIXED (8 Week) sputum culture and smear conversion with symptom resolution

The concordance of sputum culture conversion with resolution of the individual symptoms of fever, cough, productive cough, or a combination of symptoms assessed at a fixed time point of 8 weeks, which is the end of the intensive treatment phase for study 27 and 28 and the combined data set are shown in the table. There were too few patients that remained febrile at week 8, thus this endpoint did not discriminate between patients that converted sputum smear or culture. Resolution of cough appeared to best correlate with sputum culture conversion.

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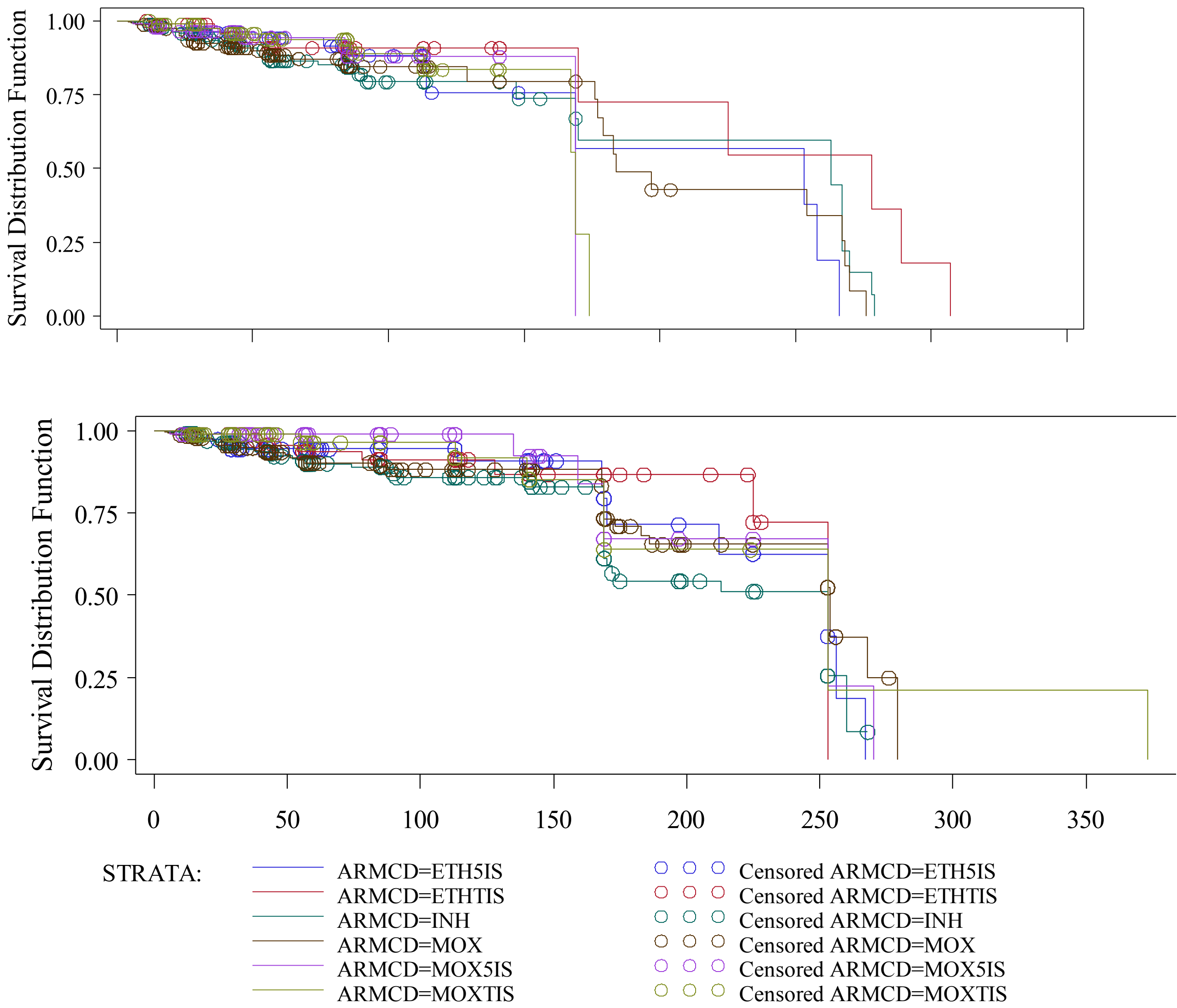
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Week 8 Symptom resolution in Study 27 and 28	Week 8 Culture conversion		Week 8 Smear conversion	
	Yes	No	Yes	No
Fever	303 (97.1%)	71 (94.5%)	259 (97.0%)	115 (95.8%)
No	9	4	8	5
Cough	237 (46.1%)	44 (36.7%)	228 (52.3%)	53 (26.8%)
No	277	76	208	145
Productive Cough	172 (46.9%)	51 (49.0%)	228 (52.3%)	53 (26.8%)
No	195	53	208	145
Fever and cough	128 (31.5%)	29 (27.6%)	128 (37.9%)	29 (16.7%)
No	279	76	210	145
At most one resolved	110 (35.8%)	36 (39.6%)	107 (44.0%)	39 (25.2%)
No	197	55	136	116

Correlation of Time-to Sputum Culture Conversion with Symptom Resolution

Shown below are the survival function analyses performed for the individual treatment arms for the time to sputum culture conversion are (top) and time to symptom resolution (bottom) performed on the combined dataset for Study 27 and 28, OR: 1.54 [1.01, 2.33]



Conclusion

This exploratory analysis of the time to sputum conversion was made feasible by the availability of data in standard terminology and format, enabling cross-study comparison of data collected for other purposes and intended for other pre-specified analyses. This serves as proof of concept that data can be re-purposed for research when standardized and aggregated in a trial repository. In this analysis, time to sputum culture conversion best correlated with resolution of productive cough at week 8 compared to cough, fever, weight loss or any combination of the latter symptoms. Time to sputum culture conversion was used as a surrogate endpoint in a recent accelerated NDA approval. Data in standard format enables cross study comparisons of efficacy endpoints and can inform trial designs for drug development. We plan a comparison of time to analyses across drug sensitive and drug resistant tuberculosis in a follow up study.