Landscape for developing a VL database

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Presented by Jeffery Smith WorldWide Antimalarial Resistance Network (WWARN)

A Database for Kala Azar?

- Why a clinical database for VL?
- Landscape of clinical data on VL?



Why a database?

Challenges

- VL is underfunded few trials and small sample sizes
- Few drugs (~5) and poorly stocked pipeline
- Existing drugs toxic/expensive/resistance threat



- Complications regional efficacy variation, HIV-VL
- Careful use and monitoring of drugs is required to maximise efficacy, reduce toxicity and minimise resistance
- Clinical trial data are 'buried' in publications or not published or delayed



Standardised Clinical Trials Database

- Provides comprehensive up-to-date clinical trial landscape
- Allows meta-analysis: improved statistics, highlight subpopulation variations and resistance
- Inform treatment allocation and future clinical trial design





WWARN Case Study

- 350 Clinical trials from 200 research institutions
- Raw data on 100,000 individuals (≈3M data points)
- WWARN Explorer
- Pooled analyses





A unique standardised database for VL?

Questions

- Are there enough trials? Are there enough data?
- Are the data from different trials comparable? Consistancy in study parameters? (e.g., dose, regimen, diagnostic tests, follow-up time and assessments?)

Assessment

- Conduct systematic review of clinical trials landscape
- Gather key information from trials (e.g., # participants, study parameters)
- Explore the potential of a database of raw data to allow for meta-analyses



Clinical Trials Registries



- Australian New Zealand Clinical Trials Registry
- ClinicalTrials.gov.
- EU Clinical Trials Register (EU-CTR)
- ISRCTN
- Brazilian Clinical Trials Registry (ReBec)
- Chinese Clinical Trial Registry
- Clinical Research Information Service Republic of Korea

- Cuban Public Registry of Clinical Trials
- German Clinical Trials Register
- Iranian Registry of Clinical Trials
- Japan Primary Registries Network
- Pan African Clinical Trial Registry
- Sri Lanka Clinical Trials Registry
- The Netherlands National Trial Register
- Thai Clinical Trials Register (TCTR)



Clinical Trials Registries

Search for 'visceral leishmaniasis' and 'kala azar'



33 registered trials

13 of 33 registered and published



Excludes duplicates and trials on vaccines, canine VL, vector control, nets, prevalence estimations, diagnostics, PK/PD, prophylaxis, and cutaneous leishmaniasis



Clinical Trials Publications

Search for 'visceral leishmaniasis' and 'kala azar'



Excludes duplicates and trials on vaccines, canine VL, vector control, nets, prevalence estimations, diagnostics, PK/PD, prophylaxis, and cutaneous leishmaniasis



Landscape of Clinical Trials

Find publications and extract data



Found 138/141 original publications

- Data extracted from abstracts for other 3 publications
- Some available at online journals
- Some available only in hard copy (from WHO Library)
- Some available only through contacting author



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Create spreadsheet of key parameters

- **Clinical trial ID**
- **Publication name**
- Authors
- Address for clinical trial
 - Journal of publication
- **Publication date**
- **Trial start and end dates**

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- Enrollment

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- Age
- Study design (single arm, comparative, dose finding
- Allocation (randomised, consecutive cohorts)
- **Study Sponsor**
- **HIV co-infection**
- Inclusion and exclusion criteria
- **Method of diagnosis**
- Test for cure method and time point
- Length of follow-up
- PubMed ID

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Clinical Trials Landscape

- 141 clinical studies on VL drugs
 - 25,865 patients (68% male)
 - Most trials enrolled less than 200
- **1,379** patients in completed, unpublished trials
- 9,802 in active trials

> Total of 37,046 patients

- Earliest publication was 1983
- Since 2000: 69 published/ 35 started
- Delay to publication: average 26 months (range 8-78)







Where and When?



Most enrolment in Indian subcontinent or Africa Gradually increasing enrolment each year





*Trials in n countries split into n trials, 1 per country

Drugs

2000-6000 patients enrolled for each drug

- Mostly from India, Africa well represented for some drugs
- Suggests large scale comparisons are possible

Most enrollments for newer drugs are recent (5-10 years)

- Easier to obtain data
- Suggests more data to come



Dose

Good consistancy in dose regimens used 1000`s of patients enrolled per dose

- Allows for pooling of data
- Allows for large scale comparisons of different dose regimens



Other

- 20mg/kg/day, 20 days
- 20mg/kg/day, 30 days
- 1 mg/kg/alternate days, 20 doses
- 1 mg/kg/day, 15 doses
- 1 mg/kg/alternate days for 15 doses
- 1 mg/kg/day, 20 doses
- 50 mg (<25 kg), 100 mg (>25kg), 2.5 mg/kg (Age <12), 28 days
 11 mg/kg/day, 21 days



Trial Design

Trials evenly split between single arm, dose-finding or comparative

Usually randomized

Patient follow:

- 6 months (~25,000)
- 12 months (~5000)

Allows pooling of data since end points consistant

Allows comparison of 12 and 6 months follow up on the scale of 1000's





Diagnostics

Diagnosis by observation of parasites in an aspirate (>76%)

- High confidence in correct diagnosis
- Do different diagnostic tests affect outcome?

End of treatment test is generally the same as for diagnosis

• 88% patients parasitologically tested for cure after treatment

End of follow up test is usually clinical (79%) or bone (10%)

Is there a difference in relapse with clinical vs parasitological test





Summary

- Individual trials are small, but many trials (141) and participants (25,865, with potential for 37,046)
- Good consistency in study design and parameters
- Trial results are difficult to access, some raw data may already be lost
- A database would improve accessibility and longevity
- Develop a visualization tool for trial results
- Meta-analysis would allow comparisons on large cohorts (1000's/arm) to improve treatment efficacy and design for future studies
- Compare outcomes based on drug, dose, country, length of follow-up, diagnosis, test for cure, etc.



WWARN's Experience



Vision: Effective and safe malaria treatment for all

Mission: To implement a collaborative platform to assess the evolution, epidemiology and public health impact of antimalarial drug resistance, and to generate the reliable evidence necessary to inform malaria control and elimination

Goal: To inform optimal use of available and future antimalarials for malaria control and elimination

Established: 2009 as a programme of the University of Oxford Centre for Tropical Medicine and Global Health





WWARN

Data Standardisation Process



Data Visualisation



🖓 Share Data | Log In | Register | Contact



Mapping summary data from antimalarial drug studies



Pooling Data for more Powerful Analyses

DHA-Piperiquine mg/kg Dosing Study Group

- 26 studies (74% of 35 studies)
- 7,072 patients between 2003–2011 (70% of 10,168)









Tools for Characterizing Drug Resistance



WWARN Parasite Clearance Estimator (PCE Tool)



Smart Surveillance



Where should we plan the next studies?

- To optimise resources
- To minimise time for recruitment
- To target the correct populations



Smart Surveillance















WWARN EQA Programme

Reference Material Programme

- Distribute certified antimalarial drug standards
- Pharmacology/PK labs
- In vitro/drug sensitivity testing
- Drug quality

Proficiency Testing Programme

- Assess performance and provide assistance
- Pharmacology labs
- Molecular labs







Challenges to Data Sharing

Data unavailable





WWARN Data Repository

- 350 clinical trials
- 200 research institutions
- Raw data on 100,000 individuals (≈3M data points)
- 2/3 of all published data since 2000



Building a VL Data Repository

- WWARN platform exists do not need to start from scratch
 - Data repository structure
 - Data upload systems
 - Data curation and harmonisation processes
 - Template data-sharing terms and agreements
 - Ethical considerations
 - Lessons learned from malaria
 - Reduces cost for establishing database



Successful Data Sharing requires...

Collaboration, partnerships, and a lot of TRUST



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www.wwarn.org