VIEWPOINT/EDITORIAL FOR TROPICAL MEDICINE AND INTERNATIONAL HEALTH

Integrating public health research trials into health systems in Africa: individual or cluster-randomisation?.

Victoria Simms[1] *, Sode Matiku[2] *, Bernard Ngowi[3], Duncan Chanda[4], Sokoine Lesikari[3], Christian Bottomley[1], Saidi Egwaga[2], Amos Kahwa[3], Lorna Guinness[1], Peter Mwaba[4], Sayoki Mfinanga[3] and Shabbar Jaffar[1 §]

1 London School of Hygiene and Tropical Medicine, London, UK
2 National Tuberculosis and Leprosy Programme, Ministry of Health and Social Welfare, Dar es Salaam, Tanzania
3 Muhimbili Medical Research Centre/National Institute of Medical Research, Dar es Salaam, Tanzania
4 University Teaching Hospital/Institute for Medical Research and Teaching, Lusaka, Zambia

*** contributed equally**

§ author for correspondence. Email shabbar.jaffar@lshtm.ac.uk

KEYWORDS: Randomised trial, cluster-randomisation, health services research, implementation research, HIV, research methods.

Main body of text 2100 words

Introduction

Health services in Africa have a very severe shortage of doctors and nurses with less than 10 doctors per 100,000 population in several countries [1] and access to health services is difficult for many patients because of high transport costs [2]. Despite these constraints, and the limited experience in delivering chronic care in Africa, antiretroviral therapy (ART) has been scaled up rapidly and about 8 million people are now on treatment [3]. In most countries, the HIV services are delivered as stand-alone vertical programmes [4].

Non-communicable diseases (NCDs) also require chronic care and their burden is rising rapidly in Africa [5, 6]. The demands for delivering chronic care services will increase substantially [7]; but African health systems are geared towards the control of acute infections [8]. Research on how to organise and deliver chronic care services in Africa will be essential in order to target the scarce resources efficiently [9]. Such research has to be integrated into health systems because its central aim is usually to estimate the effectiveness of models of health service delivery under near normal conditions in order that the findings can be generalised immediately. This is in contrast to many efficacy trials (e.g. of drugs and vaccines) which are usually implemented under parallel systems. We have previously examined the use of cluster-randomisation for a vaccine efficacy trial [10] and examined the operational and ethical issues of integrating research into routine health

service delivery [11]. Here we focus on the study design challenges, with a particular focus on whether such trials should be cluster or individually randomised.

Methods

We examine the issues using our experiences from two trials. The REMSTART trial was designed to evaluate the effectiveness of a complex health service intervention in reducing mortality among HIV-infected patients who presented with very low CD4 count to 6 government clinics in Dar es Salaam, Tanzania and Lusaka, Zambia (ISCRTN 20410413). Enrolment began in February 2012 and ended in September 2013. Follow-up is scheduled to end in September 2014. Initially, only patients with CD4 count less than 100 /µl were eligible for enrolment but the criteria were changed during the course of the trial to enrol any patient presenting with less than 200 CD4 cells /µl because of slow recruitment and because of the increasing recognition such patients had a high risk of death. Just prior to that, the criteria for initiating antiretroviral therapy changed from initiation at CD4 count<200 / µl to initiation at CD4 count<350 /µl. The World Health Organisation has recently recommended that antiretroviral therapy should now be initiated at CD4 count<500 cells /µl [12]. The change in recruitment criteria of the REMSTART trial was implemented in September 2012 in Zambia and in December 2012 in Tanzania.

The REMSTART trial intervention comprised i) rapid initiation of antiretroviral therapy, ii) screening for cryptococcal meningitis using a novel antigen test, iii) weekly home visits for 4 weeks by trained lay-workers iv) re-screening for tuberculosis using the Xpert®MTB/RIF assay (Cepheid, Sunnyvale, USA) at about 6 weeks after initiation of ART. Patients were randomised to either this intervention strategy or to standard clinic-based HIV care including ART. All participants were offered screening for tuberculosis at baseline using the Xpert®MTB/RIF assay irrespective of whether they had any symptoms or not. Participants were followed up for 12 months after enrolment. The primary endpoint was all-cause mortality.

The Jinja trial compared a home-based with a facility-based HIV care strategy in Jinja, Uganda, a predominantly rural setting [13]. The home-based strategy involved trained lay-workers visiting the patient at home on a monthly basis. ART was provided by The AIDS Support Organisation (TASO), a large non-governmental organisation. The vast majority of HIV-infected patients in the Jinja district accessed ART services at TASO. There was little provision for ART in government facilities at the time (the TASO clinic was based within the grounds of the Jinja District Hospital). Enrolment into the trial ended in December 2006, and follow-up continued until January 2009.

In both trials, lay-workers received a small salary and were supervised by clinicians and nurses based at the clinics. They received class-room training at the beginning (4 weeks in the Jinja trial, 2 weeks in REMSTART) and on-the-job training subsequently. In the home, they delivered drugs, provided adherence support, and monitored the participants for adverse events using a checklist. They referred patients if indicated and phoned a clinician based at the clinic when they were uncertain about referral. In the Jinja trial, lay-workers travelled on motorbikes while in REMSTART they travelled mostly by foot and public transport.

How should health service delivery trials be randomised? Because health care is delivered to groups (e.g. catchment populations of health centres), such trials are normally cluster-randomised with all participants in a defined cluster receiving the same mode of care - either the intervention or the control strategy [14]. Typically 6 or more clusters are randomised to each arm [15]. This design mimics the real life situation – it is how health care would normally be delivered.

One major challenge in health service trials is that patients or the health care personnel might have strong views on how health care should be delivered. For example, clinic-based care can incur substantial transport costs and home-based care involves disclosure of HIV status and stigma. In Jinja, Uganda, a single clinic visit cost the equivalent of an average 13% of man's and 20% of a woman's monthly wage and took a day of the patient's time [13]; and 19 people in the home-based care arm versus only 3 in the facility arm refused to join for fear of increased stigma . We considered that individual randomisation would be a major challenge in Jinja but the concept of neighbourhoods having the same mode of care might be acceptable. Because of similar concerns over consent, trials of breast-feeding practices have not been randomised and instead the breastfeeding groups have been defined by the choices made by the women [16]. Although, there might have been no alternative, the evidence from such studies is weaker than that from randomised trials.

One reason for randomising by clusters is to avoid interaction between people receiving different modes of care (known as contamination). For example, adherence messages delivered to people on one arm could be passed to people in the other arm, thus diluting the efficacy of the intervention. In Jinja, the TASO clinic provided the vast majority of antiretroviral therapy within a 100km radius for several years and cluster-randomisation ensured separation in the community of people receiving different models of care. However, HIV care is now available widely in Africa and achieving that separation between people on antiretroviral therapy is no longer possible. We decided to randomise the REMSTART trial individually in the belief that contamination was not a major issue because the intervention had only one behavioural component – adherence support delivered by a trained lay-worker - and contamination between participants might not influence the effects of this. Also the chances of neighbours being in the trial in different trials arms was small (we planned to enrol about 2500 participants from a total catchment population of well over 150,000 urban adults) and the chances of contamination at clinic visits would be minimised given the high degree of activities at each clinic.

Statistical power considerations. Complex interventions involve multiple components, making sample size difficult to estimate. A further complication is that trial conditions can change with changes in management guidelines or practices. Thus, it is essential that assumptions underlying the trial are reviewed periodically and trial size is adjusted where this is indicated.

Increasing the trial size in an individually randomised trial is usually relatively straightforward. In cluster-randomised trials, the number of clusters is usually the major determinant of statistical power, and adding new clusters during the course of a trial is often impractical. This is a significant drawback with cluster-randomisation. Sample size

calculations for cluster-randomised trials also require an estimate of the variability between clusters (e.g. the coefficient of variation), which is rarely known in advance.

Table 1 shows the sample size calculations for the REMSTART trial as designed and if instead this were cluster-randomised assuming coefficient of variation to be 0.1 or 0.2 [15]. Cluster-randomisation requires large increases in sample size to achieve the same level of power.

Table 1. Total number of participants needed in both groups combined in a two-arm randomised trial to detect a 40% reduction in mortality at 90% power and 5% significance level

Mortality (percent per year)		If trial is individually randomised	If trial is cluster-randomised			
Control arm	Intervention arm		12 clusters		24 clusters	
			k=0.2	k=0.1	k=0.2	k=0.1
8	4.8	2624	11005	3833	4238	3116
10	6.0	2100	8804	3067	3391	2493
12	7.2	1750	7337	2556	2825	2077
14	8.4	1500	6289	2191	2422	1780

Note, k is the coefficient of variation.

Blinding in health service trials. Blinding is rarely possible in trials of health care delivery, whether they are randomised individually or by clusters and this can be a major source of bias. It is vital that both researchers and health care staff assume equipoise; not doing so will affect the implementation of the intervention and the measurement of outcomes. It is important that health care staff are informed about the wider aspects of research, including its need and uses and that they feel that they have ownership of the research programme. It is essential that health care staff understand the concepts of bias and the need for equipoise. Providing training in research methods alone is not enough in such settings.

Control for confounding. In large, individually-randomised trials, factors that are predictive of the outcome tend to be equally distributed between the trial arms. In cluster-randomised trials, the number of clusters is usually limited and imbalance between two arms is common. For example, in the Jinja trial, 22 clusters were randomised to each strategy – 44 clusters in total [13]. By chance the number enrolled differed substantially between the two arms (859 in the home-based care arm compared to 594 for facility) and median CD4 count was significantly lower in the home-based arm. The difficulty in health service trials is that some confounders may be unknown and key known confounders such as socio-demographic variables, access to the clinic, income and ability to afford transport are all difficult to measure; therefore imbalances between arms are difficult to assess and difficult to adjust in analyses.

Data collection

Data collected by health care staff might be of poorer quality than those collected by researchers as their first priority is to attend to the clinical needs of the patient. Despite this, it is critical that there is zero tolerance of incomplete or inaccurate data. In the REMSTART trial, only essential data in simplified form were collected by clinicians and independent monitoring of the data was usually done within about 30 minutes of the patient emerging from the consultation and while the patient is still in clinic so that queries can be resolved.

Data collection can be especially problematic in cluster-randomised trials as extensive data need to be collected to adjust for the possibility of confounding. The risk of confounding is negligible in large-scale individually-randomised trials and so much greater focus can be placed on the measurement of essential outcome data.

Consistency in the delivery of standard care and in implementation of the intervention strategy. Health care delivery trials require a comparison between standard care and the intervention. However, standard care often varies between Ministry of Health guidelines and practices within clinics. Bringing change and implementing a new strategy (i.e. the intervention arm) in busy, over-stretched facilities brings further variation. In an individually randomised trial, standardisation is easier to achieve because fewer clinics are involved than in a cluster-randomised trial. In a cluster-randomised trial, resources are required in each clinic in order to standardise delivery and to monitor to what extent delivery is in accordance to protocol.

The danger in individually randomised trials is that if health care workers can see components of an intervention working well, they might be tempted to introduce it for control subjects; likewise poorly functioning components of an intervention might be dropped. In cluster-randomisation, there is much less interaction between health care staff in different facilities, such that different models of care can co-exist for longer.

In the REMSTART trial, rapid initiation of ART was perceived to be working well in the intervention arm and at the same time there was pressure to increase the number on ART in order to meet targets; consequently, the practices within the clinics changed in both countries to initiate ART rapidly in both arms of the trial. Had the trial been cluster-randomised, this change in practice may have taken longer.

Conclusions

Trials to address health service delivery questions provide valuable information to guide health care delivery but pose major challenges for health services and researchers. Blinding is rarely possible. Cluster-randomised trials mimic more closely the real life setting of how care is normally delivered, but power is reduced and control for confounding and a standardised delivery at the various clinics are more difficult to achieve. Interaction between trial participants and non-trial participants receiving different modes of care is unavoidable for chronic care services which are available in multiple settings. Control for confounding is challenging in cluster-randomised trials. Accurate data on potential confounders have to be collected but extensive data collection is impractical in busy clinic settings. In any case, the confounders in health services research are not well understood or

difficult to measure. Partnerships between researchers, health care workers, public health staff and patient groups are essential in health systems research.

REFERENCES

1. World Health Organization. World Health Report 2006 - working together for health. Geneva: World Health Organization, 2006.
2. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. *AIDS* 2012; **26**(16): 2059-67.
3. World Health Organization. Global update on HIV treatment 2013: results, impact and opportunities. Geneva: World Health Organization, 2013.
4. Munderi P, Grosskurth H, Droti B, Ross DA. What are the essential components of HIV treatment and care services in low and middle-income countries: an overview by settings and levels of the health system. *AIDS* 2012; **26**(Supplement 2): S97-S103.
5. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2224-60.
6. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization, 2009.
7. Alleyne G, Binagwaho A, Haines A, et al. Embedding non-communicable diseases in the post-2015 development agenda. *Lancet* 2013; **381**(9866): 566-74.
8. Atun R, Jaffar S, Nishtar S, et al. Improving responsiveness of health systems to non-communicable diseases. *Lancet* 2013; **381**(9867): 690-7.
9. Ebrahim S, Pearce N, Smeeth L, Casas JP, Jaffar S, Piot P. Tackling non-communicable diseases in low- and middle-income countries: is the evidence from high-income countries all we need? *PLoS Med* 2013; **10**(1): e1001377.
10. Jaffar S, Leach A, Hall AJ, et al. Preparation for a pneumococcal vaccine trial in The Gambia: individual or community randomisation? *Vaccine* 1999; **18**(7-8): 633-40.
11. Jaffar S, Amuron B, Birungi J, et al. Integrating research into routine service delivery in an antiretroviral treatment programme: lessons learnt from a cluster randomized trial comparing strategies of HIV care in Jinja, Uganda. *Tropical medicine & international health : TM & IH* 2008; **13**(6): 795-800.
12. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection – recommendations for a public health approach. . Geneva, Switzerland., 2013.
13. Jaffar S, Amuron B, Foster S, et al. Rates of virologic failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. *Lancet* 2009; **374**(9707): 2080-9.
14. Hayes RJ, Moulton LH. Cluster Randomised Trials. London: Chapman & Hall; 2009.
15. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. *International Journal of Epidemiology* 2009; **28**(2): 319-26.
16. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet* 2007; **369**(9567): 1107-16.