

UK Substudy

1. Background

The OPTIMA trial is an international multicenter randomised trial in patients with HIV infection whose antiretroviral therapy (ART) has failed and who have been exposed to all three classes of antiretroviral drugs. The trial is addressing two questions in a factorial design: (i) is a combination of at least five drugs (Mega ART) better than four or less drugs (Standard ART)? and (ii) does an antiretroviral drug free period (ARDFP) before starting a new regimen improve the chance of success? The trial is being conducted in the US by the Department of Veterans Affairs (VA), in Canada by the CTN funded by the CIHR and in the U.K by the MRC through its CTU. The trial recruitment started in June 1, 2001 and has been much slower than anticipated in all three countries.

The reasons for the poor accrual in the U.K are not related to one specific issue but rather to a combination of many factors.

First there is a much smaller than anticipated pool of eligible patients than was initially anticipated. Drugs such as Kaletra, Tenofovir and T20 have helped many 'salvage' patients. Trials of new drugs are also having difficulties in recruiting from the low CD4/highly drug experienced population but it is proving most difficult to co-enrol in these trials and OPTIMA. Sites are aware that they can enrol into OPTIMA first and then add the new drug when the new regimen is started. Agreement has been reached with Roche for patients being considered for open access T20 trial where OPTIMA would be encouraged as a strategy before starting on T20. However, some patients are unwilling to consider a drug free period before they start a new combination. Indeed a number of patients have already discontinued ART to await a new drug combination and therefore would not be eligible for OPTIMA.

Other problems include a reluctance to be randomised to both parts of the trial. Patients' preferences seem equally split between the strategies and many who would be willing to be randomised to Mega-ART or Standard ART would not consider a ARDFP and vice versa. Some doctors do not feel it is appropriate to consider both strategies in OPTIMA while they have new drugs to offer to patients. It is also felt that the patients that are potentially eligible for OPTIMA are not likely to exhibit the degree of commitment necessary to adhere to the protocol. Many of the patients who fulfil the criteria for OPTIMA come from this group.

Mega-ART is not generally prescribed in the U.K due to cost, and whilst a subvention from the NHS was gained to supplement the payments made by MRC, these payments were insufficient to cover the costs of most Mega-ART regimens. (The payment took into account the savings made when on the ARDFP.)

A wide range of interventions has been instigated to stimulate recruitment in the U.K. These include increased resources to help sites identify eligible patients, a detailed patient leaflet with a wide circulation list (4,500 were distributed, 2,700 of these were directly mailed to readers of HIV Treatment Bulletin, who are health care professionals and people living with HIV), and a new website. All doctors treating people with HIV were written to informing them of this study and suggesting a shared care option to some small centres with the aim of increasing the number of participating centres in order to ensure the widest possible access to this trial for eligible patients.

Regular contact is maintained with the sites in a number of ways. Direct telephone contact from the project manager and trial physician, mail outs, newsletters, teleconferences, investigator meetings both at international conferences and national meetings and site visits.

The U.K also has contacted 3 countries not participating in the collaboration with the view of extending the study to these countries. Only Spain are interested at present.

The TSC it was agreed to amend the total sample size for the trial from 1700 to 500 as new information from the trial itself and from other similar trials had indicated a that the original conservatively estimated event rates were too low. Even with the new smaller sample size, at the current rate, recruitment will not be completed until 2005 and there are concerns whether the U.K can realistically achieve and maintain an

accrual rate of one patient per month. At this level of recruitment it is difficult to maintain the profile of the trial and lack of familiarity with the trial procedures becomes a deterrent to many clinical centres. There is no doubt that such a slow rate of recruitment is difficult to maintain, even if the clinicians consider that the questions are still important.

2. Amendment to the trial in the U.K

At the recent meeting of the Trial Steering Committee for the OPTIMA Trial a proposal to amend the trial in the U.K was discussed with the aim of increasing recruitment. Although it may be possible to recruit one patient a month it is very difficult to sustain the enthusiasm and interest in the trials in the clinical sites and at the co-coordinating centre in the U.K.

It is clear that a number of potentially eligible patients are not joining OPTIMA because they are unwilling to accept both randomisations. It is therefore proposed that for such patients the possibility of randomisation within one of the strategies rather than both is offered. Randomisation within the 2X2 factorial design will still be the first and preferred option.

This will mean that the number of patients who will be randomised to mega-ART or standard ART will be increased to include patients who:

1. are unwilling to accept an ARDFP,
2. have already stopped ART.

Similarly patients will be randomised to ARDFP or no ARDFP who:

1. want to take (or are already taking) mega-ART,
2. do not want to take mega-ART,
3. the Trust will not fund mega-ART.

Clinicians will still encourage patients to randomise within both comparisons (option 1, See Flow sheet). If however, patients select only one comparison (option 2 or 3, See Flow sheet) the clinician will, prior to randomisation, ask the patient:

1. whether they will be taking mega-ART or standard ART if entering the ARDFP or no ARDFP comparison;
2. whether they will or will not have an ARDFP if entering the mega-ART or standard ART comparison.

The randomisation will be stratified by the chosen option and this will be taken account of in the analysis via stratification, so that for the main effects, comparison between strategies will only be made within options and not between options. Patients entering only one randomisation can only be included in that main comparison, and will not contribute to the test of interaction (synergy), e.g. whether the effect of mega-ART relative to standard ART depends on whether the treatment was preceded by an ARDFP or not.

The disadvantage of this proposal is that to answer both the questions addressed in the trial the total number of patients will have to be increased. For each patient who would have been randomised within the factorial design (Option 1) it will require two (one in Option 2 and one in Option 3) to provide the same amount of information for the main comparisons. The aim will continue to be to recruit patients to Option 1 and only to offer Option 2 and 3 where the patients and/or the clinician is not willing to accept the double randomisation.

Following the introduction of the pilot, recruitment in the UK has increased significantly.

3. Implications of the modification

The modification has no implications for the trial or protocol, except:

1. The possibility of randomisation to Options 2 or 3 will be offered to those patients and/or clinicians who are not willing to accept randomisation to the factorial design.
2. Patients choosing Option 2 will be asked to choose whether or not to have an ARDFP (or may have already had one) before they are randomised and similarly those choosing Option 3 will have to decide between Standard or mega-ART. The randomisation form will be amended accordingly.
3. The randomisation schedule will be amended in the U.K to include stratification by Options 1, 2 or 3.
4. The analysis plan will be modified to take into account the change above.
5. The Patient information sheet will be amended to give details of the choice open to potential participants.

4. Impact on the participants

As the trial will not be modified in any way apart from allowing the choice between the three randomisation options which increase patient choice, there are no specific implications for participants. All study procedures including clinical assessments, laboratory investigations and biological specimen collection will be exactly as in the original protocol.

5. Flow Chart

Design of the OPTIMA Pilot Study
Patients / Doctors choose one of the 3 OPTIONS below

