Author's response to reviews

Title: Effective recruitment of participants to a phase I study using the internet and publicity releases through charities and patient organisations: analysis of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D)

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Author's response to reviews: see over
17th December 2014

Professor Doug Altman,
Director of CSM and Cancer Research UK Medical Statistics Group,
University of Oxford,
c/o BioMed Central,
236 Gray's Inn Road,
London WC1X 8HB
United Kingdom

Dear Professor Altman,

Effective recruitment of participants to a phase I study using the internet and publicity releases through charities and patient organisations: analysis of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D)

Thank you for the opportunity to respond to the reviewers’ reports and editorial requests. We have now revised the manuscript in response to these comments. The main changes are:

- Title changed
- Abstract conclusion revised to
- Background change to include comparison to other early phase T1D studies
- Methods rewritten to include new disease duration, deprivation and financial analysis
- Analysis objectives defined clearly
- DILT1D recruitment database described and made available to other investigators
- Results rewritten to report new analysis - 2 new tables, 1 new diagram
- Discussion and conclusion revised with two new paragraphs to address new results and generalizability of recruitment strategy.

We have also addressed the reviewers comments and with a point-by-point response to their concerns in pages following.

Reviewer: Sean F Dinneen

Minor Essential revisions

Page 5, Line 1: the word registrar is incorrect; should be register.
Corrected

Discretionary Revisions

It would be useful in the Discussion to place the (enormous) effort that went into recruitment for this mechanistic study in the context of other studies of treatments to prevent or treat type 1 diabetes using
immunotherapy. The authors suggest that their analyses of patient participation are relevant to other mechanistic studies. What about their relevance to clinical trials of immunotherapy in type 1 diabetes?

Reply

We agree that it is important to share our experience with other investigators given the paucity of publications to guide them in how to utilise the internet to enhance recruitment. It would be helpful if other investigators employed these recruitment methods within the conduct of their clinical trials and evaluated their performance to determine if an active internet recruitment strategy could enhance participation in these studies.

We have changed the conclusion in the abstract

“Conclusions: Analysis of the DILT1D study recruitment outcomes illustrates the utility of an active internet recruitment strategy, supported by patient groups and charities, funding agencies and sponsors in successfully conducting an early phase study in T1D. This recruitment strategy should now be evaluated in late stage trials to develop treatments for T1D and other diseases.”

We have inserted a new paragraph in the discussion:

“Despite widespread use and access to the internet in developed countries, there is limited published data to guide investigators on how to successfully employ this media to optimise participation in clinical studies and trials. Our development of an effective internet based method to inform and engage potential participants in the DILT1D study suggests that this strategy could be generalisable to RCT’s and late stage trials to develop treatments for type 1 diabetes and other diseases. In the future we would encourage other investigators to utilise this active internet recruitment strategy prospectively to determine if it enhances participation and thereby accelerates trial conduct.”

Table 2 includes data on potential participants’ reasons for declining study involvement. It would be helpful to understand the reasons why the 45 individuals who did participate were motivated to do so. Were there any differences (eg, employment status) between those who did participate and those who declined?

We agree that this question is important. However, we did not formally record the reasons why individuals participated in the study. We have attempted to address if there were differences in the social economic status between decliners and participants by using the demographic and depravation data (see response to Colin Dayan). We found that individuals who came to the attention of the trial team from the clinic source were from the least deprived areas while there was no difference in the socioeconomic status of the areas that the internet and register potential participants lived in.
Reviewer: Lorraine Buis

Major Compulsory Revisions:

1. Background: I’m confused. You say in the last paragraph of this section that “the statistical design of the DILT1D phase I/II trial required a relatively large number of participants to be recruited to complete the study” yet you only ultimately enrolled 40. Perhaps this is my naivety regarding mechanistic trials, but this seems like a very small sample to me. I recognize that the potentially eligible sample of newly diagnosed T1D is probably relatively small at one recruitment site, so perhaps that is why you initially estimated 2 years for recruitment. I guess this is the long way of me trying to indicate that if your recruitment goal of 40 participants is what you would consider difficult to achieve, please provide some context about how many people mechanistic trials typically enroll, how many potentially eligible participants there were at your site, and how long it typically takes to hit those recruitment targets.

Reply

We have compared our recruitment rates to other phase I/II trials of IL-2 in type 1 diabetes, healthy controls and metastatic melanoma.

<table>
<thead>
<tr>
<th>index</th>
<th>Author/Year</th>
<th>Trial Reg</th>
<th>N</th>
<th>Dates</th>
<th>Rate (pts/month)</th>
<th>Patient Profile</th>
<th>Phase</th>
<th>Sites</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hwang et al. 2011 (Mol. Ther.)</td>
<td>NCT00429312</td>
<td>10</td>
<td>Mar-2007 – Feb-2008</td>
<td>1.1</td>
<td>Previously treated stage iv Melanoma Patients</td>
<td>I/II</td>
<td>&gt;1</td>
<td>SGA*, open label</td>
</tr>
<tr>
<td>2</td>
<td>Ito et al. 2014 (Mol. Ther.)</td>
<td>NCT01445561</td>
<td>22</td>
<td>Sep-2011 – Jul-2013</td>
<td>1</td>
<td>Healthy Volunteers</td>
<td>I</td>
<td>1</td>
<td>SGA, open label</td>
</tr>
<tr>
<td>3</td>
<td>Hartemann et al. 2014 (Lancet)</td>
<td>NCT01353833</td>
<td>25</td>
<td>May-2011 – April 2012</td>
<td>2.3</td>
<td>T1D</td>
<td>I/II</td>
<td>1</td>
<td>RCT</td>
</tr>
<tr>
<td>#</td>
<td>DILT1D</td>
<td></td>
<td>40</td>
<td>Apr-2013, Apr-2014</td>
<td>3.3</td>
<td>T1D</td>
<td>I/II</td>
<td>1</td>
<td>SGA open label</td>
</tr>
</tbody>
</table>

* SGA single group assignment
The early phase trials of Ito and Hartmann et al. appear to be the best comparators.

We have inserted in **background:**

“The statistical design of the DILT1D phase I/II trial required a relatively large number of participants (N=45) to be recruited to complete the study compared to previous early phase studies of ULD IL-2 therapy in type 1 diabetes (N=25)[20] and healthy individuals (N=22)[21].”

And **discussion:**

“The DILT1D trial successfully achieved enrolment of the study in a timely and efficient manner with the study completing 11 months earlier than the two year protocol specified target with a recruitment rate of 3.3 participants per month that exceeded previous studies of ULD IL-2 therapy in T1D (2.3/month) [20] and healthy individuals (1/month) [21].”

2. **Background:** You’ve done a nice job explaining the main trial (although, perhaps a little too much detail as I previously mentioned), but you fail to adequately address the purpose of this secondary data analysis. You briefly touch on it, but a more explicit statement of the goal of this secondary data analysis, along with a stronger rationale for why this manuscript contributes to the existing body of literature, would strengthen the paper overall and help provide a better frame for telling your story. The question that this manuscript attempts to address is not well defined. As it stands, this manuscript isn’t framed well enough and reads as an attempt to squeeze out an additional publication.

**Reply**

We agree with the reviewer that the description of the trial conduct may have been too detailed and have revised the methods section in light of this reviewer’s and the editorial comments. This section has now been titled “**DILT1D study outline**”

To clearly define the rationale for the manuscript we have added a section titled **“The primary objectives of the DILT1D recruitment analysis”**

“The aims of this recruitment analysis are to evaluate the performance of three pre-specified recruitment sources to optimise the recruitment strategy for the next study in the DIL programme (DILfrequency [22]) and to share our methods with the broader clinical trials community.”

3. **Results (Analysis of Trial Outcome of Participants by Recruitment Source):** I had a very difficult time following this section. I feel like either a.) more scaffolding needs to be provided for your readers in the form of additional subheads, or b.) a more logical flow of results needs to be presented; for example, providing all info pertaining to people expressing interest by modality, all people enrolling by modality, etc.
Reply

To address the reviewer concern we have added subsection to the “Analysis of Trial Outcome of Participants by Recruitment Source”

The four new subsections are:

Outcome of contacts by register:
Outcome of contacts by DILT1D study team:
Proportion of individuals declining enrolment by recruitment source:
Analysis of success of each recruitment source:

This should provide reader with the scaffolding to follow the analysis.

4. Discussion: I would like to see more attention paid in this section to take-home points that can be people understand better what this piece contributes to the literature. Also, how generalizable is this study? What are the implications for future work? shared with other researchers. Positioning this manuscript within the larger body of literature will help

Reply

We agree that it is important to share our experience with other investigators given the paucity of publications to guide them in how to utilise the intranet to enhance recruitment. It would be helpful if other investigators employed these recruitment methods within the conduct of their clinical trials and evaluated their performance to determine if an active internet recruitment strategy could enhance participation in these studies. We have inserted a new paragraph in the discussion:

“Despite widespread use and access to the internet in developed countries, there is limited published data to guide investigations on how to successfully employ this media to optimise participation in clinical trials. Our development of an effective internet based method to inform and engage potential participants in the DILT1D study suggests that this strategy could be generalisable to RCT’s and late stage trials to develop treatments for type 1 diabetes and other diseases. In the future we would encourage other investigators to utilise this active internet recruitment strategy prospectively to determine if it enhances participation and thereby accelerates trial conduct.”

5. Discussion: What were the limitations of your approach?

Reply

The main limitation of this work is that the analysis is post hoc and it is not yet clear that it can be generalised to other trial settings. This is why we have suggested that other investigators need to test the strategy prospectively and other trial types.
Minor Essential Revisions:

1. Methods: It is not clear whether you are screening individuals who are <100 days or < 2 years post diagnosis. Please clarify.

   **Reply**

   We have changed the sentence to clarify:

   “In total 45 participants with either newly (< 100 days post diagnosis) or recently diagnosed (< 2 years post diagnosis) T1D were screened”

2. Methods: Regarding the Facebook and Twitter accounts created for your study, did you do anything to actively promote your trial within those channels? For example, did you continually post status updates and tweets?

   **Reply**

   We have provided more detail on the frequency social media updates:

   “The internet was identified as a potential source of direct recruitment by the DILT1D team. The website, [clinical-trials-type-1-diabetes.com](http://clinical-trials-type-1-diabetes.com) was developed with an associated Facebook page ([facebook.com/ClinicalTrialsType1Diabetes](http://facebook.com/ClinicalTrialsType1Diabetes)) and Twitter feed ([@t1diabetestrial](http://twitter.com/t1diabetestrial)) both of which were updated on a fortnightly to monthly basis to provide content and public engagement during the study.”

3. Methods (Recruitment Data): After reading it a few times, I think I understand what you are trying to say, but the following is not very clear, “A single ‘trial outcome’ was defined for each potential participant. The five trial outcomes were:”

   **Reply**

   We have changed these statements to:

   “Each potential participant was defined as belonging to one of five ‘outcome’ categories, depending on their status after the recruitment process had ended.

   The five trial recruitment outcomes were:”

4. Results (Analysis of Trial Outcome of Participants by Recruitment Source): I liked your presentation of how many potential participants came from the ADDRESS-2 Register, followed by how many of those
responded to the contact and how many ultimately enrolled. I would have liked to see that fleshed out fully for the other two recruitment modalities.

Reply

This data for ADDRESS-2 was presented in the text since there was a recruitment phase that was not mediated by the DILT1D study team. After that point all information regarding responses, ineligibility and enrolment for the three recruitment modalities is presented in figure 2, table 1 and table 2.

5. Results (Analysis of Trial Outcome of Participants by Recruitment Source): “Final trial outcome differed according to recruitment source.” This is not clear. I think perhaps that many of the clarity issues that I find in this section may be caused by confusing terminology. Also, didn’t you say in the previous section that there were 5 possible outcomes?

Reply

We have revised the “Analysis of Trial Outcome of Participants by Recruitment Source section” to make it easier for the reader to follow. (Please see 3. in compulsory revisions).

To clarify “Final trial outcome differed according to recruitment source” has been changed to “The final trial recruitment outcome was influenced by the source of potential participants”

6. Discussion: You conclude that you successfully achieved enrolment of the study in a timely and efficient manner. As I previously mentioned, without additional context about the difficulties you anticipated in your recruitment, 13 months to recruit 40 people will not sound impressive to the majority of readers.

Reply

We have placed the success of our recruitment efforts by comparing it to equivalent mechanistic trials and placed this data in the paper for readers to review (Please see 1. in compulsory revisions)

7. Conclusions: You state that “potential participants favoured the internet...” Is it that the potential participants favoured that modality, or is it that that was the most readily accessible modality? It certainly had a broader reach, which doesn’t necessarily suggest to me that potential participants favoured the modality.

Reply

We agree that the use of the word favoured could cause confusion so we have removed it and changed the final sentence to:
“We found that most potential participants utilised the internet for making contact with the study team compared to traditional recruitment modalities and this group did not find distance or borders a barrier to participation. “

Discretionary Revisions:

1. Background: As a reader expecting to learn about recruitment strategies for a clinical trial, I found myself bogged down in the details of the trial itself. While it is important to describe the trial, I can’t help but feel that there is too much detail, which ultimately leads to clarity issues within this section.

The actual design of the trial and approach been taken to develop a new treatment for a disease is important this needs to conveyed to the reader.

Reply

We consider it is important that the reader understands background to the trial and why we have taken a mechanistic approach to the development of a new drug to treat T1D. We have as recommended by the reviewer cut down the description of the trial in the methods section.

2. Methods: Again, there is a lot of detail here about the trial itself, which detracts from the purpose of the present secondary data analysis. Personally, I’d like to see a briefer description of the main trial and its methods, and then the citation to follow-up with if I have more questions.

Reply

We have changed this section and reduced the description of the trial (Please see 2. in compulsory revisions)

3. Results (Demography of Potential Trial Participants): How does your recruitment of males and females reflect the incidence of T1D among males and females?

Reply

We have included this data in the demographics section:

“We observed a ratio of 1.9 males to 1 female potential participants in agreement with the previously reported skewing towards more male T1D patients versus female ones[31]. Similar numbers of male and female potential participants (gender known in N=314) were observed for each recruitment source as well as for the final trial outcome of participants (Figure 1a).”
4. Results (Demography of Potential Trial Participants): Was there any difference in the demography of enrolled participants across the three recruitment sources? I’m not sure if that will add anything to the overall manuscript, but I couldn’t help but wonder.

We have now analysed the demography of participants

Differences between demography of consented participants (n=45):

Gender – none (as per (3), Age – No difference:

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinics</th>
<th>Media</th>
<th>Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>6</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>30-40</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>40-50</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Χ²=1.3613; p=0.8509 (n=45)
KW test on age at contact and source: H=1.6340; p=0.4418

Duration disease: (Please see response to Colin Dayan following)

Indices of deprivation. (Please response to Colin Dayan following).

5. Title: I’m not convinced that the title accurately conveys what has been found in this manuscript. “Optimizing Recruitment” suggests to me that you iteratively changed your methods in order to maximize recruitment. The paper describes a methodology that set out to use these three modalities, and then you described what you found.

Reply

We agree and have changed title to:

“The effective recruitment of participants to a phase I study using the internet and publicity releases through charities and patient organisations: analysis of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D)’’

Reviewer: Colin CM Dayan
Major points:

1. Mention clinic recruitment figures in abstract (only register and internet figures quoted) and something about evidence or not of recruitment bias from the different sources.

Reply

We have changed the abstract to include the clinic figures so raw data from all three sources is now included in the abstract.

“Self-referral via the study website was the most popular and successful modality by which individuals registered with the DILT1D team (170/317: 54%), with the remainder being sourced from diabetes clinic (88/317:28%).”

This sentence also states what we found by analysing the data that self-referral via the web site was the most successful modality. That recruitment was “biased” towards the internet source.

2. Need to distinguish newly- (< 100 d) and recently (< 2 years) diagnosed groups in the analysis and show these figures. Specifically, this relates to whether the three approaches are equally good for incident (new-onset) versus prevalent (< 2 years) disease. Comment on which approach would need to be used for a new-onset study (< 100d).

Reply

We agree with the review and have undertaken a new analysis of the recruitment data stratified on the duration of disease from the three recruitment sources. We have made a new table 2 to illustrate this data:

<table>
<thead>
<tr>
<th>T1D duration*</th>
<th>Clinics</th>
<th>Internet</th>
<th>Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 100 days</td>
<td>24 (9%)</td>
<td>33 (12%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>&gt;3 months &amp; less than 2 years</td>
<td>56 (21%)</td>
<td>85 (31%)</td>
<td>47 (17%)</td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>1 (0.4%)</td>
<td>24 (9%)</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>
*Newly diagnosed T1D (< 100 days = 3 months) and recently diagnosed T1D (< 2 years)

^Number of individuals in each group category where data was available.

To analyse the relative success of each recruitment source in identifying newly diagnosed cases we applied a Chi squared test.

<table>
<thead>
<tr>
<th></th>
<th>Clinic</th>
<th>Internet</th>
<th>Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed - &lt;100 days</td>
<td>24</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Observed (all registered)</td>
<td>88</td>
<td>170</td>
<td>59</td>
</tr>
<tr>
<td>Expected</td>
<td>16 (28%)</td>
<td>31 (53%)</td>
<td>11 (19%)</td>
</tr>
</tbody>
</table>

\( \chi^2 = 13.2199, \text{N}=317 \text{ p}=0.0013 \).

When all participants who registered with the study team are included in the analysis the clinics appear to outperform other sources of recruitment for potential participants with disease duration of less than 100 days. However, when individuals of duration greater two years (ineligible) are excluded both the clinics (24) and internet (33) sources identified more potential participants than the register within 100 days of diagnosis. The final analysis implies that the clinic source is the most ‘efficient’ method of acquiring participants of duration < 100 days, as many more people in that category come from there whilst the register is the least efficient.

**We have made a new figure 1b** (high resolution in figures)
We have made the following changes to the text:

**Results**

Demography and duration T1D of potential study participants

“Generally trials of immunotherapies to treat newly diagnosed T1D have eligibility criteria that participants are recruited within a 100 days of diagnosis. Though this group was not specifically targeted for recruitment to DILT1D both the internet and clinic sources identified a relatively large number of newly diagnosed (ND) cases. Out of the 272 with known duration of T1D 57 (21%) ND T1D cases were identified from these sources, a number that corresponds to 23% of the eligible participants (with less than 2 years disease duration since diagnosis, N=246). Only one ND T1D participant was identified by the Register (1/272=0.4%; 1/242=0.4%) (Figure 1b), (Table 2). Overall when all potential participants (irrespective of whether duration was known) are included, the clinics sources outperform (observed versus expected: 24 versus 16), the internet (33 versus 31) or register (1 versus 11) (χ^2=13.2199, N=317 p=0.0013).”

**Discussion**

“The clinic source was found to be best at identifying newly diagnosed T1D compared to the internet or register sources. However, when ineligible individuals are excluded from all recruitment sources both the clinics and internet source identified more newly diagnosed than the register. This suggests that internet may be a good method of identifying newly diagnosed participants by self-referral for experimental medicine studies and immunotherapy intervention trials in T1D but the study team will be required to screen out a high number of ineligible participants. The register was the least successful in identify this group and this may be related to a time lag that may occur between registration on the register, and then further contact and enrolment in the actual study. It may be possible to optimise recruitment of newly diagnosed participants from the register by allowing study teams to directly contact potential participants that have joined the register.”

3. Is there any data on insulin production in the trial participants to inform future recruitment of c-peptide positive participants?

**Reply**

We did not collect data on C-peptide to establish eligibility for the DILT1D study since it was a mechanistic study and not designed to access metabolic efficacy. This paper analysed data that was collected as part of the eligibility criteria. We will include the C-peptide data of the study participants (N=40) in the analysis of the study results from DILT1D.

4. Clinic database search – on date of diagnosis? Was this routinely recorded in clinic records?
Reply

We did not carry out clinic database searches on the date of diagnosis but rather used physician, specialist diabetes nurse and self-reported dates for diagnosis of T1D. We found that participants’ accurately recalled their date of diagnosis. For the register the potential participants the date of diagnosis was provided by the register and was confirmed with then confirmed with the potential participant by the study team.

In the methods section, in the DILT1D study outline we have stated specifically how the date of diagnosis was established

“The date of diagnosis of T1D was established by referring physicians, diabetes specialist nurses, review of register records and self-reporting by potential participants.”

We have clarified in the methods section, management and strategy, where the data for the date of diagnosis was recorded to establish eligibility:

“The DILT1D recruitment and contact management database was explored for identifying relationships between the recruitment source, the study outcomes, demography, date of diagnosis and time to recruitment of potential participants.”

5. Can we have baseline demographics as a table in the main article – age, distance from Trial site, gender, duration of diabetes broken down by recruitment source. Can we include HbA1c, socioeconomic class, other family member with diabetes if available, to understand bias that may be introduced by different recruitment approaches (or not).

Reply

We agree and have inserted the following table as table 1 in the main article:

Table 1: Baseline demographics of registered potential participants for DILT1D stratified by recruitment source.

<table>
<thead>
<tr>
<th>Baseline demographics</th>
<th>Clinics</th>
<th>Internet</th>
<th>Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>N=88; N=84*&lt;br&gt;30 (24 – 37.25)</td>
<td>N=170; N=121&lt;br&gt;26 (19 -35)</td>
<td>N=59; N=48&lt;br&gt;31 (23.75 - 35)</td>
</tr>
<tr>
<td>Gender (F/ M)</td>
<td>N=89; 29/ 59</td>
<td>N=170; N=168&lt;br&gt;63/105</td>
<td>N=59; N=58&lt;br&gt;16/42</td>
</tr>
<tr>
<td>Distance from trial site (km)</td>
<td>N=88; N=76&lt;br&gt;23.62 (9.302 – 51.450)</td>
<td>N=170; N=72&lt;br&gt;150.30 (71.89 – 478.2)</td>
<td>N=59; N=54&lt;br&gt;123 (69.21 – 202.50)</td>
</tr>
</tbody>
</table>
*Number of individuals where data is available
^ Median (range)

We have made the following changes to the text:

Methods

Socioeconomic analysis
Socioeconomic data (e.g. employment, education and income status) on individual potential participants was not available since this was not part of the eligibility criteria of the study. Instead, area level socioeconomic indicators (SEI) were applied to potential participants where an English postcode was available. As such, data should be interpreted as ‘participants coming from areas of a particular deprivation status’. The reliance on full postcode data meant that the Index of Multiple Deprivation was available for 47% of potential participants (149/317), the majority of missing data due to the absence of such information from web sourced participants (28/170 – 16%) whilst clinic (70/88 – 80%) and register (51/59 – 86%) groups were more complete.

Results
Demography and duration T1D of potential trial participants

“Potential participants who were identified by the web and internet sources lived further from the trial site (H = 93.5475, N = 202; p < 0.0001). While those from the clinic source came from less deprived areas (H =10.1629, N = 149); p = 0.0062) having a lower deprivation score compared to the other source though this analysis is limited by the lack of postcode data available for the internet source (Table 1).”

HbA1c and family history data is not available since it was not part of the eligibility criteria of the DILT1D study
6. **Table 1 – need to also quote as percentage of the subjects recruited by this route, not just total numbers.**

Reply

We include percentages in this table and renumbered the table in light of other data requested:

<table>
<thead>
<tr>
<th>Source</th>
<th>Age</th>
<th>Thyroid Disorder</th>
<th>Diagnosis</th>
<th>Duration*</th>
<th>Drug</th>
<th>Malignancy &lt; 5yrs</th>
<th>Medical History</th>
<th>Pregnancy/ Breast Feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinics</td>
<td>2 (2.3%)</td>
<td>3 (3.4%)</td>
<td>2 (2.3%)</td>
<td>11 (13%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Register</td>
<td>1 (1.7%)</td>
<td>2 (3.4%)</td>
<td>1 (1.7%)</td>
<td>2 (3.4%)</td>
<td>1 (1.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Internet</td>
<td>25 (15%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>24 (15%)</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

7. **Page 11 para 3. Recalculation of the success of different sources of recruitment corrected for volume of participants – please show individual %s as well as chi-squared value.**

Reply

We have now included the individual % as well as the chi-squared value. This value has been included in the paragraph.

“However, if the total number of individuals contacted by the Register (N = 477) is included for calculating the success rate of the Register, these proportions appear to differ with the proportion of success from the Register to be the smallest (10/477:6%).”

8. **Page 11 last paragraph. Further analysis and comment on distance travelled by source please e.g. (1) were they offered local accommodation for some or all of the duration of the study e.g. from Scotland, Ireland and France – and how did this impact on costs. (2) were there any issues on verifying medical info e.g. from GPs/clinics for distant participants (esp from other countries) (3) Overall travel/accommodation costs for different routes of recruitment and comment vs rapid trial completion**
Reply

All participants were offered reimbursed stipend for reasonable expenses incurred by their participation in the study (e.g. travel, parking, meals, accommodation and child care costs)

(1) Participants were offered accommodation around the study visit but not for the duration of the study. As expected the local recruitment form the clinic sources was less expensive than that from the register (national) and web (national and international).

<table>
<thead>
<tr>
<th></th>
<th>Clinics</th>
<th>Internet</th>
<th>Register</th>
<th>Analysis (K-W ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expenses (£)</td>
<td>N=13; 268.6 (133.6 – 346.2)*</td>
<td>N=19; 767.4 (439.4 - 1413)</td>
<td>N=10; 787.7 (298.2 - 1042)</td>
<td>H =12.2084; p =0.0022</td>
</tr>
</tbody>
</table>

*median and range
42 individuals claimed expenses

We have now included this data in the text:

The Internet as a recruitment tool to extend the geographical reach of DILT1D

“The internet (median: range) £767.4 (439.4 -1413)) and register (£787.7 (298.2 -1042)) participants claimed more expenses than the local clinic participants (£268.6 (133.6 – 346.2)).”

(2) We did not encounter any difficulty verifying medical information from other countries

(3) We agree that this analysis would be interesting but it is difficult to carry out since we only know what we have done on the study and when the study completed. However, comparison with other early phase studies in type 1 diabetes suggests that our recruitment rate was increased by facilitating recruitment of participants that did not live in the vicinity.

Please see response to reviewer Lorraine Buis (question 1)

9. Claimed in discussion that distance was not a barrier – but this was still a greater issue for the register and internet than the clinic participants (as expected).
We have clarified this statement and focused on the results of our data analysis. **We have changed the sentence to:**

“A risk was that the study would not recruit to schedule but we found that use of a single study site did not impede to enrolment and each recruitment source identified participants from different geographical areas.”

10. Please provide data on missed study visits/non-completion of the study and did this depend on recruitment source/distance.

There were only three missed visits, two from clinic source (20 km & 7 km), one from website sources (62 km).

**We have included this data in:**

**The Internet as a recruitment tool to extend the geographical reach of DILT1D**

There were three missed visits for the entire study, two from clinic sources (20 km & 7 km), two from internet source (62 km).

11. Why did the initial internet post only “work” once – the surge Jun-Aug as not repeated. Was this not posted twice? Was it not required?

The most effective post was the University and Wellcome Trust press release this leading to July-August surge. The success of this post was due to the number of different web outlets that picked up on this post especially the online magazine science news. The web response to this post is **shown in figure 4b and shows an increase in refers from all web sources.** This media release was not posted again since its effect was to identify most of the study participants while the other post and events maintain on line interest.

12. Note on time commitment issues for Register participants – suggests that they might be made aware of this earlier/when they register – ie many do not expect to commit time in future to research studies….they signed up for a one-off questionnaire and blood sample. The comment on which study team approached them first is also important.

We agree and it may be helpful for registers to undertake similar recruitment analysis of member entering interventional trials to optimise recruitment to these studies.

**We have also added the following sentence to the discussion:**

“It may be possible to optimise recruitment of newly diagnosed participants from the register by allowing study teams to directly contact potential participants that have joined the register.”
13. **Were there any particularly flexible arrangements – e.g. weekend study visits? – that made a difference in this study (and made distant travel easier)**

There was a decision to conduct home/work visits after the first ten participants had been recruited based on the tolerability of the drug. The protocol needed to be amended and only visits 4-8 were allowed as home visits.

![Figure 7. Proportion of available visits taken at home](image)

The number of home visits increased as the study progressed but the study recruited well over its entire duration so it is difficult to say what impact the home visits had.

14. **Press releases were important and were most effective as they access many outlets – can you say more about where they went to? E.g. how many newspapers picked the press release up? Any tips to getting it picked up? Can this only really be done once (as the topicality and news-worthiness wear off)?**

As far as we are aware no traditional press or media picked up on the press release and post. All posts were found by individuals from the internet due to their spread to other websites (Figure 4). Our experience suggests that a single well timed media release that will be picked up by many internet outlets may be the best strategy. However different posts may target different groups such as the Diabetes UK post that led to an increase in referrals from the clinics suggesting that health professional were better targeted by this post.
Editorial requests

1. Please include the date of registration for each trial registration number at the end of the Abstract.

Inserted

“Trial registration: NCT01827735 4th April 2013, ISRCTN27852285 23 March 2013, DRN767 21 January 2013”

2. Please include a statement in your Methods section explaining that you obtained informed consent from each participant.

Inserted.

“Potential participants interested in enrolling in the study were provided with a patient information sheet and an informed consent form to review. Participants were given a minimum of 24 hours to consider the information provided and then where contacted to determine if they remain interested in participating in the study or if they had any further queries. Interested potential participants were then invited to attend for an appointment where the CI or delegate discussed the study with the participant and then invited them to provide informed consent.”

3. Please move your ethical approval statement to the Methods section.

Moved to end of methods section

Ethical approval and sponsorship: 

“The trial was sponsored by the University of Cambridge and Cambridge Universities Hospital NHS Foundation Trust. Ethical approval for the study was granted by the Health Research Authority, National Research Ethics Service, England (13/EE/0020) on the 18th February 2012.”

4. Please mention each author individually in your Authors?

Changed to:

“FWL was the chief investigator of DILT1D, designed and managed the recruitment strategy for trial and co-wrote the manuscript. JH co-wrote the manuscript and designed the DILT1D database. NMW developed the data management systems. DG, JH, KA and COB identified participants, explained the study to them and assisted with enrolled to the study. CG assisted with recruitment from the DGAP study and set of PIC sites. SN provided expert advice regarding publicity and recruitment. JB coordinated participant travel and accommodation. ME co-wrote the manuscript and performed the statistical analysis. JAT assisted with the design of the study and drafting of the manuscript. All authors read and approved the manuscript.

DG, JH, KA and COB are research nurses, their roles were identical so to avoid repetition we have mentioned them together.
5. For your additional files, please ensure that you list the following information after your reference section in your manuscript:

**Additional Files**

**Name: Additional file 1**

File name: add_file_1.csv  
Format: data file - csv  
Title: DILT1D website referral groupings  
Description: List of all study website referral sources and associated grouping category

**Name: Additional file 2**

File name: add_file_2.xlsx  
Format: data file – tabular data – xlsx  
Title: Table A1. Not-permitted by recruitment source  
Description: Summary of criteria for assignment to non permitted outcome group

**Name: Additional file 3**

File name: add_file_3_DILT1D_recruitment_CONSORT_flow.pdf  
Format: .pdf  
Title: Recruitment consort flow diagram  
Description: Recruitment consort diagram

**Name: Additional file 4**

File name: add_file_4_DILT1D-recruitment-CONSORT-2010-Checklist.pdf  
Format: .pdf
Title: CONSORT 2010 checklist of information to include when reporting a randomised trial MS: 5052849341417871: Research

Description: Completed consort CONSORT 2010 checklist

We look forward to hearing from you regarding our submission.

Yours sincerely,

[Signature]

Dr Frank Waldron-Lynch and Professor John Todd