Is the public-private mix approach increasing tuberculosis case notification in Azad Jammu and Kashmir, Pakistan? A cross-sectional study [version 1; peer review: 1 approved with reservations, 1 not approved]

Mumtaz Hussain1, Razia Fatima2, Zahida Qasim1, Aashifa Yaqoob2, Ahmed Wali3, Sabir Abbasi1, Sabira Tahseen2

1State TB Reference Laboratory, State TB Control Program, Azad Jammu and Kashmir (AJK), 10250, Pakistan
2National TB Control Program, Islamabad, 44000, Pakistan
3Provincial TB Control Program, Quetta, Balochistan, 87300, Pakistan

Abstract

Background: Pakistan ranks among high tuberculosis (TB) burden countries, with about 200,000 missing TB cases. Despite significant increase in case detection and treatment outcomes through public-private mix (PPM) globally, the contribution of the private sector may vary in different parts of Pakistan.

Methods: This was a cross sectional study conducted in state of Azad Jammu and Kashmir (AJK), Pakistan. The study was a retrospective record review of routine TB notification and treatment outcomes for 2015 to 2016 in districts with and without a PPM approach. The study was conducted in all districts of AJK, including all public and private health facilities. Intra-district comparison in PPM supported districts was also carried out.

Results: Total notified TB cases during 2015-16 were 11479. Districts with PPM support has notified 5882 (51.24%) of TB cases while districts without PPM support contributed 5597 (48.87%). Pulmonary clinical diagnosis was higher in PPM supported districts (45.43%) as compared to districts without PPM support (31.11%). Notification of extra pulmonary TB cases was lower in PPM supported districts (1454) as compared to districts without PPM support (1877; 33.54%). Unfavourable treatment outcomes (treatment failure, died, lost to follow-up) was higher in PPM facilities (5.84%).

Conclusion: The study shows minimal increase in TB case finding through the PPM approach. While this is an important aspect in END TB strategy, this needs more careful evaluation.

Keywords

Public Private Mix, Tuberculosis, case notification, treatment outcomes, AJK-Pakistan

This article is included in the TDR gateway.
Corresponding author: Mumtaz Hussain (mumtazbiotech@hotmail.com)

Author roles: Hussain M: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft Preparation; Fatima R: Resources, Supervision, Writing – Review & Editing; Qasim Z: Supervision, Visualization; Yaqoob A: Formal Analysis, Visualization, Writing – Review & Editing; Wali A: Writing – Review & Editing; Abbasi S: Supervision; Tahseen S: Supervision

Competing interests: No competing interests were disclosed.

Grant information: This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2019 World Health Organisation. This is an open access article distributed under the terms of the Creative Commons Attribution IGO License, which permits copying, adaptation and distribution in any medium or format for any purpose, provided the original work is properly cited, a link is provided to the license, and any changes made are indicated. Any such copying, adaptation and distribution must not in any way suggest that World Health Organisation endorses you or your use.

How to cite this article: Hussain M, Fatima R, Qasim Z et al. Is the public-private mix approach increasing tuberculosis case notification in Azad Jammu and Kashmir, Pakistan? A cross-sectional study [version 1; peer review: 1 approved with reservations, 1 not approved] F1000Research 2019, 8:35 (https://doi.org/10.12688/f1000research.17062.1)

First published: 09 Jan 2019, 8:35 (https://doi.org/10.12688/f1000research.17062.1)
Introduction
Tuberculosis (TB) remains a major public health problem, as it is the leading cause of death from a single infectious agent. Globally, about 10 million people developed TB disease with 1.3 million TB deaths annually. TB case notification is challenging as there was a 3.4 million gap globally between notified and incident cases. To ensure universal access to quality TB services is a major challenge due to lack of systematic engagement of all health care providers, especially in the private sector.

The public sector plays a major role in control of TB in Pakistan. More than 70% of total case notification was from public sector in 2017. Similarly, a study from India showed that the public sector has contributed 84% in TB case notification. In addition, the role of the public sector in management of TB was assessed in Thailand and it was concluded that 90% of TB cases were diagnosed and treated in public health facilities, while the private sector contributed only 10% in case notification and treatment.

The public-private mix (PPM) approach has been suggested by the World Health Organization to engage all health care providers. PPM approach was tested in 23 countries from 1999 to 2000 and there was an increase in case detection rate and treatment outcome remained above 85%. Evidence suggests that PPM has the capacity to achieve increased case notification, increased treatment outcome and more importantly it also improves patient satisfaction.

Several studies have been conducted in the region for estimation of cost effectiveness and the impact of PPM on case detection and TB management. These studies suggested that PPM is a promising model with increased case notification and improved treatment outcome. However, PPM intervention can vary in terms of accessibility, cost effectiveness, acceptability and quality.

About 80% of TB patients in Pakistan attend private sector facilities for their initial diagnosis and management and most of them are not reported to the National TB Control Program. Pakistan lists among countries with the highest number of unnotified TB cases. In 2006, Pakistan adopted PPM model which has been gradually scaled-up. The contribution of PPM in all case notification in Pakistan has been reported to be up to 18%. Studies from Pakistan have revealed that PPM can play a substantial role in achieving the targets of treatment success rate and case detection. Majority of TB cases which are managed by private sector, are not notified to National TB Control Program. Although the referral of presumptive TB cases is higher (70.9%), but only 29.1% are treated.

All studies conducted in Pakistan focused the role of private sector but there is limited data available for inter-district and intra-district comparison. There is a need to compare the PPM districts with public sector districts, which are in close vicinity and with minimal geographical differences. Therefore, this study provided an inter-district as well as intra-district comparison in intervention districts in terms of case notification and treatment outcomes. This study also provided the overall contribution of public and private sector in terms of TB case notification and treatment outcomes.

Methods
Study design
This was a cross-sectional study based on the retrospective review of routine data of State TB control program from 2015 to 2016.

Study setting
Azad Jammu and Kashmir (AJK) is a self-governing state in Pakistan with a population of 4.045 million. Administratively it is divided into three divisions and ten districts. The total area of AJK is 5134 square miles (13,297 square km). The topography of the area is mainly hilly with high mountains, valleys and stretches of plains. The rural urban ratio is 88:12. State TB Control Program is actively participating in the control of TB.

PPM approach was adopted in 2011 in three districts and then scaled up to four districts in 2015. PPM approach in AJK is carried out by Sub-Recipient with Global Fund’s Principle Recipient.

PPM approach in four districts (Bagh, Kotli, Mirpur and Bhimber) comprises almost half of the population of AJK. In these four districts, the General Practitioner (GP) model has been adopted and currently 73 GPs and 14 diagnostic laboratories work actively in these districts.

Data variables
TB case notification including pulmonary and extra pulmonary cases was assessed. TB treatment outcomes (cured, treatment completed, lost to follow-up, treatment failure, died and not evaluated) was compared between districts.

Data sources and collection
Data was collected from district reports. TB case notification report and TB treatment outcomes report was used for retrospective data analysis. Data collected at district level was verified and validated with TB registers available at each TB facility in all districts.

Data analysis
Data was collected from district reports and then entered into Epi-Data software (version 3.1 EpiData Association, Odense, Denmark). Data was analysed and percentages were obtained. Case notification of districts with and without PPM support was validated with TB registers available at each TB facility in all districts.

Ethical consideration
Written approval (849/DHS-CDC/18) was obtained from the TB program manager of AJK-Pakistan. As secondary data was used, there was no direct involvement of patients/human subjects in this study.
Results
Total notified TB cases during 2015-16 were 11479. Districts with PPM support has notified 5882 (51.24%) of TB cases while districts without PPM support contributed 5597 (48.87%). The percent change due to PPM intervention was 2.48%. Bacteriologically positive TB cases notified by PPM districts were 1954 (33.22%). Districts without PPM support notified 1979 (35.36%) bacteriologically positive TB cases. PPM supported districts notified 2672 (45.43%) pulmonary clinically diagnosed TB cases. Clinically diagnosed TB cases in districts without PPM support was 1741 (31.11%). The percent change in pulmonary clinically diagnosed TB cases was 14.32%. Total notification of extra pulmonary TB cases was 3133. PPM supported districts contributed 1256 (21.35%) as compared to districts without PPM support 1877 (33.54%). The percent change in extra pulmonary TB cases was -12.18% (Table 1).

Intra-district comparison of PPM supported districts is shown in Table 3. The PPM TB health facilities contributed 15% of TB case notification with a higher proportion of clinical diagnosis and lower proportion of extra pulmonary TB cases. Public health TB facilities contributed 24% of extra pulmonary cases, while PPM TB facilities contributed only 6.41%. Total TB case notification by PPM supported districts was higher in Mirpur, followed by Bhimber, Bagh and Kotli.

TB treatment outcomes among PPM supported districts were analysed. Unfavourable treatment outcomes (treatment failure, died, lost to follow-up) was higher in PPM facilities (5.84%).

Discussion
It is evident from the study that the public sector remained the major contributor in TB case notification; the public sector notified 85% TB cases while the private sector contributed 15% only. In our study, inter-district comparison showed that case notification in districts with and without PPM support was almost the same with minimal difference. Pakistan has prioritized the PPM approach and there was a 30% increase in case detection rate in 2017. Data from Pakistan suggested that TB
case notification has been increased due to involvement of private health care providers. Similar studies from Pakistan also suggested that TB case notification has been improved due to involvement of private health care providers. All these studies were conducted in PPM supported districts, but there is limited data available to compare PPM supported districts with non-PPM districts (public sector only).

In this study, pulmonary TB clinical diagnosis was higher in PPM support districts with a percent change of 14.32%. This showed that the private sector is relying more on X-ray based diagnosis or clinical diagnosis without referring the presumptive TB cases for laboratory investigation. A prevalence survey in Pakistan also showed that the majority of pulmonary TB cases are diagnosed by radiography in the private sector. A study conducted in Karachi-Pakistan also concluded that the numbers of TB cases from the private sector are clinically diagnosed and there is a need for strengthening reliance on TB laboratories for screening of presumptive TB cases. Therefore, the private sector is relying more on X-ray based diagnosis rather lab based diagnosis. Laboratory based diagnosis in the private sector is limited and more than half of all presumptive TB cases in the private sector is referred to the public sector for diagnosis.

In this study extra-pulmonary TB case notification in districts with PPM support is lower with a percent change -12.82%. Extra pulmonary TB case notification is usually difficult and needs extra investigation with high quality tests. GP model needs more

---

**Table 1.** Inter district comparison of tuberculosis (TB) case notification in districts with and without public-private mix (PPM) approach in Azad Jammu and Kashmir, Pakistan (2015–16).

<table>
<thead>
<tr>
<th></th>
<th>Grand total</th>
<th>Districts with PPM support (a)</th>
<th>Districts without PPM support (b)</th>
<th>Change (a-b; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total notified TB cases</strong></td>
<td>11479</td>
<td>5882 (51.24)</td>
<td>5597 (48.76)</td>
<td>2.48</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bacteriologically positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>3536</td>
<td>1812 (30.81)</td>
<td>1724 (30.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Relapse</td>
<td>324</td>
<td>114 (1.94)</td>
<td>210 (3.75)</td>
<td>-1.81</td>
</tr>
<tr>
<td>Retreatment</td>
<td>73</td>
<td>28 (0.48)</td>
<td>45 (0.80)</td>
<td>-0.33</td>
</tr>
<tr>
<td><strong>Clinically diagnosed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>4134</td>
<td>2528 (42.98)</td>
<td>1606 (28.69)</td>
<td>14.28</td>
</tr>
<tr>
<td>Relapse</td>
<td>97</td>
<td>58 (0.99)</td>
<td>39 (0.70)</td>
<td>0.29</td>
</tr>
<tr>
<td>Retreatment</td>
<td>182</td>
<td>86 (1.46)</td>
<td>96 (1.72)</td>
<td>-0.25</td>
</tr>
<tr>
<td><strong>Extra pulmonary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>2968</td>
<td>1202 (20.44)</td>
<td>1766 (31.55)</td>
<td>-11.12</td>
</tr>
<tr>
<td>Relapse</td>
<td>39</td>
<td>14 (0.24)</td>
<td>25 (0.45)</td>
<td>-0.21</td>
</tr>
<tr>
<td>Retreatment</td>
<td>126</td>
<td>40 (0.68)</td>
<td>86 (1.54)</td>
<td>-0.86</td>
</tr>
</tbody>
</table>

---

**Table 2.** Inter district comparison of tuberculosis treatment outcomes in districts with and without public-private mix (PPM) approach in Azad Jammu and Kashmir, Pakistan (2015–2016).

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>Grand total</th>
<th>Districts with PPM support (a)</th>
<th>Districts without PPM support (b)</th>
<th>Difference (a-b; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>3606</td>
<td>1820</td>
<td>1786</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>7189</td>
<td>3772</td>
<td>3417</td>
<td>0.09</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>54</td>
<td>11</td>
<td>43</td>
<td>-2.91</td>
</tr>
<tr>
<td>Treatment failed</td>
<td>47</td>
<td>26</td>
<td>21</td>
<td>0.19</td>
</tr>
<tr>
<td>Died</td>
<td>463</td>
<td>221</td>
<td>242</td>
<td>-0.10</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>120</td>
<td>32</td>
<td>88</td>
<td>-1.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Public TB care facilities, n (%)</th>
<th>PPM TB facilities, n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB case notification total</strong></td>
<td>5009 (85.0)</td>
<td>873 (15.0)</td>
<td>5882</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriologically positive</td>
<td>1749 (34.92)</td>
<td>205 (23.48)</td>
<td>1954</td>
</tr>
<tr>
<td>Clinically diagnosed</td>
<td>2060 (41.13)</td>
<td>612 (70.10)</td>
<td>2672</td>
</tr>
<tr>
<td>Extra pulmonary</td>
<td>1200 (23.96)</td>
<td>56 (6.41)</td>
<td>1256</td>
</tr>
<tr>
<td><strong>Treatment outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured</td>
<td>1634 (93.42)</td>
<td>195 (95.12)</td>
<td>1830</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>3149 (96.6)</td>
<td>604 (90.42)</td>
<td>3753</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>8 (0.16)</td>
<td>7 (0.80)</td>
<td>15</td>
</tr>
<tr>
<td>Treatment failed</td>
<td>19 (0.38)</td>
<td>8 (0.92)</td>
<td>27</td>
</tr>
<tr>
<td>Died</td>
<td>185 (3.69)</td>
<td>36 (4.12)</td>
<td>221</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>14 (0.28)</td>
<td>23 (2.63)</td>
<td>37</td>
</tr>
<tr>
<td><strong>TB case notification by districts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bagh</td>
<td>1473 (84)</td>
<td>286 (16)</td>
<td>1759</td>
</tr>
<tr>
<td>Bhimber</td>
<td>906 (80)</td>
<td>222 (20)</td>
<td>1128</td>
</tr>
<tr>
<td>Mirpur</td>
<td>870 (78)</td>
<td>239 (22)</td>
<td>1109</td>
</tr>
<tr>
<td>Kotli</td>
<td>1760 (93)</td>
<td>126 (07)</td>
<td>1886</td>
</tr>
</tbody>
</table>

Districts with PPM support: n=4.


attention for selection criteria in Pakistan. Different studies from Pakistan showed that there is a significant knowledge gap between public and private sector doctors, and private doctors have lesser knowledge for diagnosis and management of TB.

TB treatment outcomes are one of the major indicators for assessing a successful TB control program. A study showed that AJK had reported a 95% treatment success rate. The proportion of unfavourable TB treatment outcomes, died, TB treatment failure and lost to follow-up, were 3.8%, 0.1% and 0.2% respectively. Our study also showed similar results with minor difference in public and private TB health facilities. Overall TB treatment success rate was above 95% in public TB health facilities. The proportion of unsuccessful TB treatment outcomes was higher in PPM facilities (5.84%).

Our study showed that TB case notification through PPM was only 15% in PPM supported districts, but there was no such significant difference when PPM supported districts were compared with non-PPM districts (public sector only). A comparative performance of public and private health sector in low and middle income countries also support our study that the public sector is more efficient, accountable and medically effective than the private sector. In Pakistan there is need of more stringent selection criteria for GP selection to improve their involvement in TB control. PPM is an important approach to achieve global TB targets; however it could be affected by contextual characteristics in different areas.

The strength of the study is that it compares PPM supported districts with other districts (non-PPM supported). Previous studies in Pakistan focus on few districts while this study covers a whole region of AJK, and all districts and health facilities were included in this study.

The limitation of our study is the reliance on program data. Accuracy and completeness of the data cannot be assured. There could be many reasons for deaths, and it is important to know that deaths occur due to TB rather that to another reason.

Conclusions
The study showed minimal increase in TB case finding using the PPM approach. While this is an important aspect in END TB strategy, this needs more careful evaluation. The public sector is contributing effectively to TB case notification and has better TB treatment outcomes. Therefore, there is a need to strengthen the public sector.

Recommendations
Although the PPM approach is promising and is included in the END TB strategy, our study showed that the public sector is more efficient than PPM in terms of case notification and
treatment outcomes. Public sector of AJK is comparable with PPM supported districts, with more good indicators. It could be further improved by monitoring and evaluation. PPM approach needs stringent selection criteria so that it could perform more efficiently. Contextual characteristics need to be addressed while implementing PPM.

Data availability

**Underlying data**

Figshare: Dataset 1: Is the public-private mix approach increasing tuberculosis case notification in Azad Jammu and Kashmir, Pakistan? A cross-sectional study. This data set contains the TB case notification and TB treatment outcomes from both public and private health facilities of AJK-Pakistan, https://doi.org/10.6084/m9.figshare.7388036.v1.26

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Grant information

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR).

Funders

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR). The training model is based on a course developed jointly by the International Union Against Tuberculosis and Lung Disease (The Union, Paris, France) and Médecins Sans Frontières (MSF, Geneva, Switzerland). The specific SORT IT programme that resulted in this publication was implemented by the National Tuberculosis Control Programme of Pakistan, through the support of the Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund, Geneva, Switzerland). The publication fee was covered by the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR).

References

15. Tb N, Program C: Public Private Mix Experience for TB control. TB Situation in Pakistan. Reference Source

Page 7 of 11
Olusola Adedeji Adejumo
Department of Community Health and Primary Health Care, Lagos State University Teaching Hospital, Lagos, Nigeria

Thank you for asking me to review this manuscript. While this is an interesting topic the authors assumed that the prevalence of TB will be the same in PPM supported and Non-PPM supported district. That is why they compared them. This assumption may not hold. Factors like the presence of slums and socio-economic status of peoples may not be evenly distributed.

In conducting this study, authors should have compared the Case notification rates in the PPM supported districts before and after the commencement of the PPM scheme. In that way, all potential bias will be corrected for. This is a major flaw for me in this manuscript

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
No
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Methods:

- Study setting: The authors should describe more on the PPM approach and the public sector approach especially for case finding and notification. Is there any difference in case finding strategy between PPM and public sector? If yes, it needs to be addressed in the discussion. For example, if the public sector is using active case findings and PPM is only passive case finding, case notification would be different. A table or diagram showing PPM model in Pakistan would be helpful to understand the context since different countries use different models of PPM.

- Data sources and collection: It is suggested to elaborate more about district reports; whether data from private sectors were included and completeness and proportion of missing data in reports and register.

Results:

- It is necessary to clarify some findings especially for comparison between PPM and non-PPM and intra-district comparison. E.g. in the 2nd paragraph of the results, Table 2 shows loss to follow up was less in PPM districts. But in the last sentence of the results, it stated that unfavorable treatment outcome was higher in PPM facilities. Clear description and comparison should be made.

- It is surprising to see 15% in PPM facilities and 85% in public facilities for case notification (Table 3) while 80% of TB patients in Pakistan attend private sector for initial diagnosis. Under-reporting from the private sector and incompleteness of district reports might be the reasons. These interpretations should come up clearly in the discussion session.

Discussion and Conclusions:
• Other possible factors contributing to case notification and treatment outcomes need to be addressed and discussed.

• Caution needs to be taken for the conclusion saying that the public sector is contributing effectively to TB case notification and has better treatment outcome just by using programme data. Weakness in reporting and recording at PPM clinics and also the public sector may also need to be considered.

• Recommendations: The authors stated that the PPM approach needs stringent selection criteria. However, there is no evidence or findings related to selection criteria in the results section to support this recommendation.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is acceptable. However, I would suggest this as a short report rather than a research article. I have significant reservations, as outlined above.

Is the work clearly and accurately presented and does it cite the current literature? 
Yes

Is the study design appropriate and is the work technically sound? 
Yes

Are sufficient details of methods and analysis provided to allow replication by others? 
Partly

If applicable, is the statistical analysis and its interpretation appropriate? 
Not applicable

Are all the source data underlying the results available to ensure full reproducibility? 
Partly

Are the conclusions drawn adequately supported by the results? 
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis, Health Systems Research, Public Private partnership, operational research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:
• Your article is published within days, with no editorial bias
• You can publish traditional articles, null/negative results, case reports, data notes and more
• The peer review process is transparent and collaborative
• Your article is indexed in PubMed after passing peer review
• Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com