Citizens for Affordable,
Safe & Effective Medicine
CASEM

To

October 25, 2021

Dr. Mansukh Mandaviya,
Minister for Health & Family Welfare,
Government of India, 348-A,
Nirman Bhawan, Maulana Azad Road,
New Delhi – 110 011.

Dear Dr. Mandaviya,

Sub: Regarding the working of the Clinical Trial Registry of India (CTRI)

By way of introduction, I am a public health activist and the Founder of Citizens for Affordable, Safe & Effective Medicine (CASEM) which aims to be a collective of like-minded individuals working towards ensuring that the medicines supplied to India and other countries are affordable, safe and effective. I have formerly worked in the Indian pharmaceutical industry and was responsible for exposing the regulatory violations at Ranbaxy Laboratories after which the company was prosecuted and fined $500 million dollars by the United States Food and Drug Administration (USFDA).

Since the end of my whistle-blower lawsuit against Ranbaxy in 2013, I have been engaged in advocacy aimed at strengthening the drug regulatory framework in India. This includes multiple petitions and reports that I have submitted to your Ministry with various recommendations to improve drug regulation in India.

I am writing to you with reference to the function and oversight of the systems and processes that govern the conduct of clinical trials in India. The Clinical Trials Registry of India (CTRI), which is tasked with maintaining a record of all clinical trials being conducted in India was setup in 2007. The Registry has introduced a certain degree of transparency into the conduct of clinical trials in India; however, it is lacking in certain aspects ranging from design to accuracy of information it stores to quality of disclosure needed for transparent conduct of clinical trials. There are two aspects to this issue. First is the quality of the information that is entered into the Registry.

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The second issue is the governance of the process that allows the investigators, sponsors, regulators and researchers to make sure the information curated by the registry is accurate, timely and complete in order to make institutions conducting clinical trials accountable to regulators and the general public. This petition addresses both these issues. I have made certain recommendations in the attached paper, based on conversations with experts, on how the CTRI and the oversight of Ethics Committees can be revamped so as to be more useful for both the medical community and the general public. I request you to take the necessary action on these recommendations.

Sincerely,

Dinesh Thakur

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A petition to reform the workings of the Clinical Trials Registry of India

The Clinical Trials Registry of India (CTRI) was setup in 2007 for the purpose of capturing data about clinical trials being conducted in India. The Registry is hosted by the National Institute of Medical Statistics, which is a part of the Indian Council of Medical Research (ICMR). Despite the many scandals in the conduct of clinical trials in India, it was not compulsory for clinical trials to be registered on the CTRI until the promulgation of the New Drugs and Clinical Trial Rules, 2019.[1] While this registration requirement was a welcome move, a lot more needs to be done to ensure that institutions conducting clinical trials actually submit accurate and complete information to the CTRI. Only with the submission of accurate and complete information can the CTRI achieve its aim of guaranteeing transparency of clinical trials. Ensuring high standards of transparency in the clinical trials ecosystem is critical to building confidence in Indian clinical trials and preventing scandals in the Indian clinical trial ecosystem.

In the past, there have been several controversies related to the conduct of clinical trials in India. In 2013, there was the scandal during the clinical trials over the HPV vaccine, which was documented in detail by the Department-Related Parliamentary Standing Committee on Health and Family Welfare.[2] Subsequently, during the COVID pandemic, several questions were raised about the manner in which clinical trials for drugs like Favipiravir, Itolizumab, Virafin and 2DG were designed, approved and conducted by the DCGI.[3]

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[1] New Drugs & Clinical Trials Rules 2019, Rule 25(v).

[2] Department-Related Parliamentary Standing Committee on Health and Family Welfare, *Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by Path in India (Department of Health Research, Ministry of Health and Family Welfare)* (Seventy-Second Report) (RS 2013).

[3] Priyanka Pulla, 'Scientists Criticize 'rushed' Approval of Indian COVID-19 Vaccine without Efficacy Data' (*Science*, 5 January 2021) <https://www.science.org/content/article/scientists-criticize-rushed-approval-indian-covid-19-vaccine-without-efficacy-data> accessed 25 October 2021; Priyanka Pulla, 'Is Favipiravir Good for COVID-19? Clinical Trial Says No, Press Release Says Yes' (*The Wire Science*, 25 November 2020) <https://science.thewire.in/the-sciences/favipiravir-glenmark-open-label-trial-primary-endpoints-efficacy-cure-times-misleading-press-release/> accessed 25 October 2021; Dinesh Thakur and S P Kalantri, 'The Many Questions about Favipiravir' *The Hindu* (25 June 2020) <https://www.thehindu.com/opinion/op-ed/the-many-questions-about-

Questions were also raised by the integrity of the clinical data collected at People's Hospital in Bhopal, one of the study sites for development of Covaxin.[4] The process by which Emergency Use Authorization in Clinical Trial Mode was granted to Bharat Biotech for Covaxin has been questioned across the board by experts.[5]

Much of this dysfunction is directly related to the way we accept, curate and manage clinical trial data in our trial registry, the CTRI. A 2019 study of global clinical trial registries by Nicholas DeVito at Oxford University rates India's Clinical Trial Registry as one of the least effective in helping conduct ethical clinical studies in the country.[6] As demonstrated by this study, the CTRI is not just the least competent technically in terms of functionality it provides, it is also mired by lack of an effective governance structure in place. No wonder therefore that the results of those who use this platform to conduct and oversee clinical studies run into significant ethical and structural issues that have been so effectively documented during the Covid-19 pandemic.

1. **The problem of incomplete and inaccurate information on the CTRI:** One of the problems currently with the CTRI is the fact principal investigators do not always provide complete or accurate information about their trials during the process of registering with the CTRI.

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favipiravir/article31908725.ece> accessed 25 October 2021; Dr Jammi Nagaraj Rao, 'Four Months After Itolizumab "Trial" and 9 Million Infections Later – No Progress' (*The Wire Science*, 6 December 2020) <https://science.thewire.in/health/itolizumab-trial-preprint-paper-results-intention-to-treat-analysis-statistically-insignificant/> accessed 25 October 2021; Ronak Borana, 'DCGI Approves Virafin for Moderate COVID. Where's the Evidence It Works?' (*The Wire Science*, 24 April 2021) <https://science.thewire.in/the-sciences/zydus-virafin-pegylated-interferon-alpha-2b-india-dcgi-approve-covid-trial-methods-flaw/> accessed 25 October 2021; Ronak Borana, 'India's Drug Regulator Has Approved DRDO's New COVID Drug on Missing Evidence' (*The Wire Science*, 12 May 2021) <https://science.thewire.in/the-sciences/dcgi-drdo-2-dg-covid-19-treatment-phase-2-3-trials-shoddy-evidence/> accessed 25 October 2021.

[4] Priyanka Pulla, 'Explained: Is the Data From Covaxin Trial's Bhopal Site Tainted?' (*TheQuint*, 9 February 2021) <https://www.thequint.com/coronavirus/explained-is-the-data-from-covaxin-trials-bhopal-site-tainted-bharat-biotech-icmr> accessed 25 October 2021; Priyanka Pulla, 'Scientists Criticize 'rushed' Approval of Indian COVID-19 Vaccine without Efficacy Data' (*Science*, 5 January 2021) <https://www.science.org/content/article/scientists-criticize-rushed-approval-indian-covid-19-vaccine-without-efficacy-data> accessed 25 October 2021.

[5] Krishna N Das, 'India's Approval of Homegrown Vaccine Criticised over Lack of Data' *Reuters* (3 January 2021) <https://www.reuters.com/article/health-coronavirus-india-covaxin-idINKBN2980BN> accessed 25 October 2021.

[6] Nicholas J DeVito, 'Results Reporting at ICTRP Data-Provider Registries: A Protocol for a Cross-Sectional Audit Study' (2019).

The failure to provide complete or accurate information completely belies the purpose of making it mandatory for all clinical trials to be registered on India. The inaccuracies and incomplete information span a range of fields on the CTRI. For example, a lot of studies do not accurately list the "type of study" or the "sponsor of the study". More worrying, are the number of trials where the CTRI records either incomplete or missing information. A few such examples are as follows[7]:

(a) A clinical trial which made an informal reference to an EC, rather than its proper name: CTRI/2018/05/014249;
(b) A clinical trial for which no EC was listed: CTRI/2017/05/008477;
(c) A clinical trial where the EC fields only listed the names of the sites, which is equivalent to the EC not being listed: CTRI/2020/05/025254;

There are two reasons for the existence of incomplete or inaccurate information on the CTRI. The first is the divided responsibility between ICMR and the DCGI. While ICMR is responsible for maintaining the CTRI database, it does not appear to have any powers to scrutinise the accuracy of the information. On the other hand, is the DCGI, which, while responsible for approving all applications to conduct clinical trials, does not have any powers over the CTRI itself. The second problem is the lack of any legal sanctions under the law penalising the submission of incorrect or incomplete information to the CTRI.

Ideally, the law should be amended to make it clear that ICMR is responsible for maintaining the integrity of data on the CTRI. In order to discharge this responsibility, it should be given the power to blacklist principal investigators if the information submitted to the CTRI is either inaccurate or incomplete. The DCGI should be given concurrent legal powers to stop a clinical trial if the information provided to the CTRI is inaccurate. Another way to ensure that institutions submit all the relevant data to the CTRI is to design the CTRI in such a way that more 'fields of information' are compulsory, without which a clinical trial cannot be successfully registered on the CTRI.

Whether by legal or technical means, it is absolutely necessary for the Ministry of Health to create a strategy to ensure the integrity of all data on the CTRI so as to build confidence in the Indian clinical trial ecosystem.

[7] Mounika Pillamarapu, Abhilash Mohan and Gayatri Saberwal, 'An Analysis of Deficiencies in the Data of Interventional Drug Trials Registered with Clinical Trials Registry - India' (2019) 20 Trials 535.

2. **Redesigning the CTRI to capture better and more accurate information:** A second problem with the CTRI pertains to the manner in which it has been designed and the information that it captures. A few such problems identified by academics in the field are as follows:

   (a) **A lack of clarity in the classification of study types:** Unlike other registries which mention specific fields of study that have to be selected (for e.g. the clinical trial registry in the U.S. has 11 categories: Behavioral, Biological, Combination Product, Device, Diagnostic Test, Dietary Supplement, Drug, Genetic, Other, Procedure, and Radiation) the Indian CTRI offers a free-text field, meaning that any information can be inputted by institutions registering for clinical trials. As a result, a compilation of the CTRI reveals the following as the top 5 entries in the CTRI: (1) drugs (2732 or 22%), (2) Not Available (884, 7%), (3) Surgical/Anesthesia (850, 7%), (4) Ayurveda (737, 6%), and (5) Cross Sectional Study (684, 5%).[8]

   (b) **Internal inconsistencies:** Academics studying the accuracy of the CTRI have reported that there are several inconsistencies in the data, especially on the issue of the country in which the trial is taking place or the phase of the study. Ideally, the registry should have been designed on the basis of logic rules to improve accuracy of the information. This is not the case with the CTRI thereby creating confusion on the country in which the trial is being conducted. Similarly, for the stage of trials, even when the chosen option is Bioequivalence/Bioavailability Study, it is classified as having Phase I, II, III etc. when it is well known that such studies do not have different phases. These issues can be resolved relatively easily by the adoption of logic rules during the design of the database. For example, if the field *Country of Recruitment* is entered as India, then all the other fields regarding 'global' status of the trial should automatically be declared "not applicable" or disappear. Similarly, if "Bioequivalence/Bioavailability Study" is selected, there should be no question of choosing different phases.

   (c) **The presence of non-standard information:** Another problem with the CTRI is the presence of non-standard information when it comes to city names. For example, for trials being conducted in Mumbai, the following classifications can be found in the CTRI: North, North East, North West, South,

[8] ibid.

South West, West, Mumbai (Suburban). A simple solution for this is to use a 'drop down' menu of cities which will then make it possible to conduct an easier data analysis of the resulting information. Similarly, the names of same institutions and individuals may be represented in different ways in different trials. A way to standardise such data would be for individuals and institutions to register and create an ID, as is the case with ORCID ID etc. for academic publications. This will better help in tracking the number of trials being conducted at various organisations by different principal investigators.

(d) **The presence of messy data:** A general complaint against the CTRI is that much of the data in it is messy making it difficult to facilitate any detailed data analysis. This problem can be partly resolved through the use of drop-down menus, logic rules, mandatory fields. There is however no substitute to having better scrutiny of all entries by the staff responsible for administering the CTRI.

(e) **An audit trail for the data in the CTRI:** The current implementation of the CTRI database captures the most recent changes made to the trial data; it does not have an audit trail of what changed, by whom and when. A good example of why this is important is studies with multiple end-points. The initial study design may specify multiple endpoints for a study protocol, which is later amended based on what the interim analysis shows. This leads to cherry-picking study data as has been observed with many studies currently registered in the database. An audit trail for each data element in the CTRI databse will allow us to see what changes were made by the sponsor subsequent to the start of the study and if such changes have a material impact on study outcome? This is particularly important for studies with multiple end-points where sponsors tend to choose the one most favorable to their commercial interests.

Another example is where registrants can remove a site from their CTRI entry without specifying the reason for such removal. This happens when the ethics committee for that particular site for example, could have objected to the protocol or asked for amendments. There is currently no way to capture such information in the CTRI. Creating an audit trail on the present CTRI database will allow the database to capture and track such changes in a manner that can be viewed by third parties also.

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(f) **Internal validation of data in the CTRI:** Merely registering a study in the CTRI does not mean it is a valid study for execution before it is scrutinized by the regulator. Internal validation and controls coupled with a workflow between the CTRI and the review of an application to conduct a clinical study by the CDSCO is must in order for this data to be ethically used. In the absence of such a control, mere entry of study design, however faulty, can be used by unscrupulous actors to justify claims that are not grounded in science.

3. **Mandating greater disclosure requirements under the law for clinical trial data:** One key issue pertaining to clinical trials, which has so far received little attention in India, is the issue of requiring all institutions conducting clinical trials in India to mandatorily and proactively disclose the data generated during those clinical trials irrespective of whether the trial succeeded or not. In 2017, ICMR signed a MOU with the WHO to comply with the 24 WHO specified data elements in the primary registry. One of these elements is "summary results", which includes data collected at the start of the study for all participants, treatment outcomes etc. The MOU calls for the study's summary results to be posted in the registry within 12 months of completing the study. In 2021, there is still no such functionality within the CTRI. A recent study found that 45% of 133 cancer related clinical trials registered in the Clinical Trials Registry of India (CTRI) up to February 2016, and that had completed recruitment, hadn't published their results as of June 2020.[9]

   Analysis conducted by Cochrane author Denny John, adjunct Prof at Amrita Institute of Medical Sciences and Research in Kochi found that of the 2935 randomised controlled trials (RCTs) registered in CTRI between 2009 and 2015, less than 3% had posted links to their published papers as of August 2018. Researchers also searched databases like PubMed and Google Scholar, and emailed study authors. They found published papers for a total of 755 of the registered RCTs, with over 74% of the trials remaining unpublished.[10]

   Traditionally, even the western pharmaceutical industry and research universities have resisted sharing clinical trial information publicly. This position however changed radically after a ruling, in 2020, by an American court

[9] Shreya Dasgupta, 'The Mystery of India's Missing Clinical Trial Results' (2020) 371 BMJ m4835.

[10] ibid.

in the case of *Siefe* v. *HHS*[11] which required all clinical trial sponsors to comply with a decade old law that required the sharing of such data with the Clinical Trials registry in the U.S.[12] This mandatory disclosure requirement in American law was fuelled by scandals wherein American pharmaceutical companies suppressed safety information from clinical trials for drugs that later turned out to be controversial. Currently under Indian law, there is absolutely no requirement to make this data publicly available. Any request for disclosure of such information under the RTI Act is likely to be met with an outright rejection by the regulator on the grounds that such disclosure would violate the prohibition in the RTI Act against disclosure of data that is likely to violate the commercial confidence of any private party. This position of law needs to change in India so that all underlying data for all clinical trials conducted in India are mandatorily published on the CTRI website so as to ensure that pharmaceutical companies cannot pick and choose the kind of clinical trial data that is made public. Such an approach to data transparency would vastly improve the confidence of the medical community in clinical trials and new medicine.

4. Overhaul the Governance Process for data curated by the CTRI:

A key function of the regulator is to provide functional oversight to the Institutional Ethics Committtees which are mandated to ensure proper conduct of clinical studies at various sites across the country. There have been multiple instances where these Ethics Committes are either perfunctory or just not functional leading to gross violations of Good Clinical Practices. Since the membership and function of these Ethics Committees is intricately tied into the data that is entered into the CTRI, it is important to revisit their formation and function when we look at reforming the CTRI holistically.

Registration of the Institutional Ethics Committees is done by the CDSCO. The regulator maintains a database of all approved Ethics Committees across the country. Ideally, there should be a one-to-one map between the CDSCO database

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[11] *Seife & Lurie vs U.S. Department of Health and Human Services et al*, No. 1:18-cv-11462, 2020 WL 883478 (S.D.N.Y. 24 February 2020).

[12] Lev Facher, 'Federal Judge Rules Clinical Trial Sponsors Must Publish a Decade's Worth of Missing Data' (*STAT*, 25 February 2020) <https://www.statnews.com/2020/02/25/clinical-trial-sponsors-publish-missing-data/> accessed 25 October 2021; Lev Facher, 'Following Court Ruling, NIH Warns Drug and Device Companies to Post Missing Trial Data' (*STAT*, 4 August 2020) <https://www.statnews.com/2020/08/04/nih-warns-missing-clinical-trial-data/> accessed 25 October 2021.

and the CTRI so that studies that are not being overseen by approved Institutional Ethics Committee cannot be registered in the CTRI.

Enrollment of patients in a study and compliance with Informed Consent is a key responsibility of the Ethics Committee. Since the CTRI contains information about how many patients were enrolled at each study site and whether they qualify the study's inclusion/exclusion criteria, the role of the Ethics Committee in such activity becomes critical. Also, these committees are responsible for assessing adverse events, compensation to victims of fraud, reimbursements etc. They also maintain oversight over the Principal Investigator of the study at that particular site and therefore are partially responsible for the quality of the data generated during the course of the study at that site. Meetings of the Ethics Committees, their membership, their action items ought to be adequately captured in the CTRI allowing patients enrolled in such studies to see how their interests are being protected by the guardian who is empowered to do so. This will also improve the quality and fidelity of the data captured by the CTRI.

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