

Protecting citizens' health: Transparency of clinical trial data on medicines in the EU

Key points:

- Data secrecy perpetuates reporting bias, where the benefits of medicines are overrated and harms downplayed.
- Full transparency of clinical trial data reinforces evidence-based medicine. Increased public knowledge on the real effects of medicines contributes to rational use and the protection of public health.
- Clinical trial data cannot be considered commercially confidential information. Human health is an overriding public interest.
- Public access to trial data can safeguard patient confidentiality.
- Clinical study reports, including duly de-identified patient-level data, from all clinical trials, must be made publicly available.

Policy paper

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Health Action International (HAI) is an independent, global network, working to increase access to essential medicines and improve their rational use through research excellence and evidence-based advocacy.

Introductionⁱ

Estimates indicate that 5% of all hospital admissions are caused by an adverse drug reaction (ADR)¹ and that ADRs are the fifth most common cause of hospital death.² Discussions on the safety of medicines have intensified due to recent drug withdrawals in Europe. Two of the cases relate to the recommendation of the European Medicines Agency (EMA) to withdraw the diabetes drug benfluorex (Mediator®)³ and the decision by the French medicines regulatory agency to withdraw cyproterone acetate/ethinyl estradiol (Diane 35®).^{ii 4 5 6} These decisions were taken because of associated adverse health events.

This policy paper argues that deficiencies in the current model for reporting scientific research increase patients' exposure to the risk of an adverse drug reaction.⁷ Prevailing practices of 'publication bias' – i.e. studies are published or not depending on their results- and the selective non-reporting of outcomes within published studies prevent the full effect of a medicine from publicly known.⁸ In fact, reporting bias, a common phenomenon in biomedical literature, results in the overestimation of the benefits of a medicine and an underestimation of the harms.^{9 10} It is estimated that only half of all studies first presented as abstracts have been published in full¹¹ and that positive trial data is twice as likely to be published when compared to negative results.¹²

Reviews of previously unpublished, detailed, clinical trial data by independent researchers have often contributed to a better understanding of the risk-benefit profile of medicines.^{13 14 15} For example, the independent meta-analysisⁱⁱⁱ of trials for the diabetes medicine rosiglitazone (Avandia®), which included unpublished trial data, was critical in demonstrating that the risk of myocardial infarction (heart attack) and cardiovascular induced death were significantly increased.^{iv 16} Independent reviews of clinical trial data are therefore of utmost importance in medicines safety assessment. Indeed, they can bring additional insight onto pharmaceutical therapies and thereby contribute to evidence-based medicine^v.

Researchers have long been calling for medicines regulatory authorities to disclose the clinical data which are being withheld, mainly on the grounds of commercial confidentiality.¹⁷ In 2007 members of

ⁱ On-going discussions on the disclosure of clinical trial data at the EU level, in the context of the EU Clinical Trials Regulation, focus mainly on disclosure of clinical data from trials intended to be used for obtaining a marketing authorisation. This paper will address this issue. However, the suggested policy recommendations in the last section go beyond this scope. Ideally, *all* clinical trials on medicines must be registered and full clinical trial data, from *all* trials, should be made immediately publicly available following the end of the trial.

ⁱⁱ After its suspension in May 2013 by the *Agence Nationale de Sécurité du Médicament et des Produits de Santé*, Diane 35 had to be re-authorised in France following a legally binding decision of the European Commission on 25 July 2013. The Commission's decision follows a previous recommendation of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC found that the benefits of the medicine outweigh its risks in certain patient groups. The Commission's decision is subject to some restrictions, including: Diane 35 and its generics can only be prescribed as a second-line treatment for acne; a number of surveillance measures have to be implemented and patients better informed about risks of thromboembolism.

ⁱⁱⁱ Use of statistical techniques in a systematic review to integrate the results of included studies. <http://www.cochrane.org>

^{iv} The EMA recommended the withdrawal of the medicine from the European market (Press release, EMA/585784/2010 September 23, 2010). In the US, an FDA advisory committee agreed in June 2013 to ease the restrictions on the use of Avandia that it had previously imposed. This decision has been highly criticised by consumer organisations. According to Wolfe SM from Public Citizen's Health Research Group: 'Unfortunately, in the interval since the EMA ban, more than 135,000 people used Avandia in the U.S., likely resulting in hundreds of preventable injuries and deaths'. Wolfe SM, 'Avandia: a drug that should be banned'. *Public Citizen* (Statement, last update June 7, 2013). <http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3908>

^v The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. <http://www.cochrane.org>.

the Nordic Cochrane Centre^{vi} lodged a complaint with the European Ombudsman^{vii} against the EMA for its refusal to release clinical trial data on two anti-obesity medicines.^{viii} Setting an important precedent, the Ombudsman ruled in favour of the complainants by concluding that neither the requested trial protocols nor the clinical study reports contained information that could be classified as commercially confidential.^{18 19} In part as a result of this landmark case, in 2010 the EMA adopted a more open policy on access to documents and it has since released some two million pages of information. The Agency discloses clinical trial data on request once the decision-making process for the medicinal product in question has concluded. It has also committed to proactively disclosing these data -i.e. not subject to prior request- either through its website or other sources of publication.^{20 21 22}

However, a potentially serious setback to the recent advances in access to trial data and the EMA's plans for proactive publication is posed by the upcoming ruling from the European Court of Justice (ECJ). For the first time since its implementation in 2010, the EMA's policy on access to documents is being challenged in court. At the start of 2013, the pharmaceutical companies AbbVie and InterMune lodged lawsuits against the regulatory agency over its decision to grant access to non-clinical and clinical information about one of their medicines.^{ix 23 24} Both companies base their appeal on the grounds that disclosure of such data would harm their commercial interests. Despite the EMA's commitment to pursue its policy of openness in the context of the interim rulings,^x researchers have since reported some situations of denied access to trial data.^{25 26 27}

Meanwhile, the European Commission, the European Parliament and the Council are revising the Clinical Trials Directive, which sets out the rules governing the conduct of clinical trials on medicinal products in the EU. Hence, in July 2012, the Commission published a proposal for a Regulation with the objective of fostering the EU's attractiveness in clinical research and increasing harmonisation amongst Member States.^{28 29} Provisions regulating access to trials data are widely debated aspects of the present proposal.^{xi}

The consolidation of recent advances on data transparency and the achievement of public access to full sets of trial data now depend on what happens at all these levels. If public health is to be protected, it is vital that the outcomes of on-going policy and legal debates support full transparency of clinical trial data. Indeed, increased public knowledge on the effects of medicines, both good and bad, is crucial to strengthen evidence-based medicine and the protection of public health.

^{vi} The Nordic Cochrane Centre is an independent research and information centre that is part of The Cochrane Collaboration, an international network of individuals and institutions committed to preparing, maintaining, and disseminating systematic reviews of the effects of health care. <http://www.cochrane.dk/>

^{vii} The Ombudsman investigates allegations of maladministration by EU institutions, bodies, offices and agencies, excluding ECJ, and provides non-binding recommendations in light of his/her examination.

^{viii} Rimonabant (Acomplia®) and orlistat (Xenical®).

^{ix} AbbVie's rheumatoid arthritis drug Humira® (adalimumab) and InterMune's Esbriet® (pirfenidone) medicine for idiopathic pulmonary fibrosis.

^x Interim rulings from the General Court of the EU prohibit the EMA from releasing the concerned documents in the context of the two court cases, until the Court gives a final ruling. However, third party requestors have reported denied access to trial data not related to any of the two law cases. For more information on the interim decisions and the EMA's response see: Order of the President of the General Court 25 April 2013 In Case T-44/13 R; Order of the President of the General Court 25 April 2013 In Case T-73/13 R at http://curia.europa.eu/jcms/jcms/Jo1_6308/; EMA *European Medicines Agency receives interim decision of the General Court of the EU on access to clinical and non-clinical information*. (Press release April 30, 2013).

^{xi} For more information, see Murray J. 'Clinical trials directive: The Parliament's political dilemma'. *EurActiv.com* (Opinion article, last update April 19, 2013) at <http://www.euractiv.com/health/european-parliament-clinical-tri-analysis-518898>; Euractiv 'Clinical trials debate shifts from research to transparency ahead of EU vote'. (last update May 2, 2013) and Euractiv 'MEPs give resounding 'yes' to new clinical trial rules' (last update May 31, 2013) at *EurActiv.com*.

Clinical study reports: a hidden and untapped source of data

As mentioned above, the independent review of detailed clinical trial data is critical, since it can reveal the true benefits and harms of medicines. Different sources of trial data can provide independent researchers with information about a particular trial, its purpose, methods and results. But the question remains; which is the most detailed source of information? It is often claimed that Clinical Study Reports (CSRs) offer the most comprehensive data on each clinical trial.^{30 31 32} Indeed, when compared to other common sources of information, such as registry reports and journal publications, these documents do provide the highest reporting quality, both on methods and outcomes.^{xii 33}

A clinical study report is a key component of the dossier that has to be submitted to drug regulatory authorities in an application for marketing authorisation. This document is prepared by the pharmaceutical industry following the structure of the E3 guideline developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.³⁴ According to this guideline, CSRs should include amongst others, the study protocol, statistical methods, summarised trial results as well as case report forms and patient data listings (including individual efficacy response data and adverse event listings) in the appendices. In practice, not all the appendices are systematically submitted to drug regulatory authorities. In the case of the EMA, this information (including some data at patient level) is only submitted on request by the agency.³⁵

In spite of the detailed information provided in CSRs, which can be thousands of pages long, the documents are not usually publicly accessible. CSRs have been referred to in this regard as representing “a mostly hidden and untapped source of detailed and exhaustive data on each trial.”³⁶ Secrecy is even greater in the case of patient-level data even when properly anonymised. Unfounded concerns about commercial confidentiality (or that patient confidentiality would be compromised) have for too long prevented full disclosure of clinical study reports and raw data.

Disclosure of clinical study reports: patient confidentiality can be safeguarded

Personal data protection in the EU is governed by Regulation (EC) 45/2001³⁷ which concerns the processing of personal data by the Community institutions. It is also governed by national data protection laws implementing Directive 95/46/EC.^{xiii 38} The Clinical Trials Directive requires that EU rules on personal data protection must apply to the subjects of clinical trials.³⁹ Thus, according to EU regulations, patient information included in the application for drug marketing authorisation to regulatory authorities needs to be submitted in non-identifiable form.⁴⁰ According to good clinical practice guidelines, participants in clinical trials are assigned a unique identification number.

Concerns have been expressed regarding the possibility of the release of information allowing potential re-identification of trials’ participants.⁴¹ The European Ombudsman addressed the question of patient confidentiality in its examination of the Nordic Cochrane Centre vs EMA case. In relation to the assessed clinical study reports and trial protocols, the Ombudsman found that: “Neither the requested documents nor other information in the public domain appeared to allow a link to be made between a given identification number and a particular patient, thus making it possible for him/her to be identified”.⁴² Moreover, independent researchers that have obtained access to a broad set of CSRs, including raw data, noted that nothing they had seen so far corroborates the claim from industry that the

^{xii} A registry report is a study summary of trial results posted by the sponsor, voluntarily or on a mandatory basis, in an online database. Journal publications contain a study’s summary and are voluntarily submitted for publication by the trial sponsors. Both are publicly available - journal publications often subject to a charge - but are much shorter than a CSR and less detailed. In B. Wieseler, MF Kerekes, V Vervoelgyi et al. ‘Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports and journal publications’. *BMJ* 344:d8141 (2012).

^{xiii} In January 2012 the Commission published a proposal for a comprehensive reform of The EU’s 1995 data protection rules. On-going legislative process.

non-release of patient-level data is motivated by concerns over patients' confidentiality.⁴³

According to EMA's regulators, "standards for deidentifying personal data are available and continue to evolve to ensure adequate protection".⁴⁴ In exceptional cases, for example in rare disease trials, additional measures might need to be implemented to avoid re-identification. However, in these situations, the following interpretation by the Data Protection Working Party^{xiv} on the concept of personal data, enshrined in Directive 95/46 EC, must to be considered:

"(...) a mere hypothetical possibility to single out the individual is not enough to consider the person as "identifiable". If, taking into account "*all the means likely reasonably to be used by the controller or any other person*", that possibility does not exist or is negligible, the person should not be considered as "identifiable", and the information would not be considered as "personal data".⁴⁵

Given the fact that rare diseases are often under-researched, it is all the more important to ensure that available scientific data is shared. In general, in order to allow for accurate re-analysis of trial data, de-identification has to apply in ways that patient confidentiality is upheld while the detail and robustness of the data maintained.

Commercial confidentiality: a major and unjustifiable barrier to data transparency

Clinical trials are of course, an essential phase of the drug development process. Their outcomes are crucial in the assessments undertaken by drug regulatory authorities to judge whether a medicine should be allowed on the market.

The pharmaceutical industry claims that CSRs contain commercial confidential information (CCI) and that public disclosure of such documents jeopardises their commercial interests.^{46 47} Despite recent advances in data transparency, withholding information on the grounds of commercial confidentiality is still a major barrier to the access to clinical trial data. Indeed, it is the basis of the legal challenge by AbbVie and InterMune to the EMA's new access to documents policy. In particular, AbbVie claims that data disclosure would violate their "fundamental right to the protection of confidential commercial information".⁴⁸ Similarly, InterMune contends that the EMA has failed to properly take into account its duty to follow its policies on the importance of protecting commercially confidential information.⁴⁹

The argument that clinical trial data contains CCI is inconsistent with the findings of the European Ombudsman in the context of its assessment of the Nordic Cochrane Centre v EMA case. After examining the requested documents, the Ombudsman concluded that neither the CSRs nor trial protocols contained information that could be classified as trade secrets, commercial confidences and/or intellectual property and that their disclosure could not undermine commercial interests.

The legal basis on access to documents in EU law is enshrined in Article 15 of the Treaty on the Functioning of the EU (TFEU). The Treaty grants EU citizens the right to access documents of the EU institutions, bodies, offices and agencies.⁵⁰ This right is further developed in Regulation (EC) No. 1049/2001 on public access to European Parliament, Council and Commission documents. The main purpose of this Regulation is to "give the fullest possible effect to the right of public access to documents".⁵¹

^{xiv} The Data Protection Working Party has been established by Article 29 of Directive 95/46/EC. It is an independent EU Advisory Body on Data Protection and Privacy. Its tasks are laid down in Article 30 of Directive 95/46/EC and in Article 15 of Directive 2002/58/EC.

The protection of commercial confidentiality is embedded in Article 4(2) of Regulation 1049/2001 as an exception to document disclosure^{xv}. However, it is important to note that the same article states that this and other exceptions cannot be applicable in the presence of an “overriding public interest in disclosure”. Concerning the scope of ‘overriding public interest’, legal basis for this question can be found in the TFEU, which contains an existing list of derogations to the four freedoms^{xvi} for a number of overriding public interests.⁵² In particular, regarding the free movement of goods, restrictions to this principle can apply on the grounds of “public morality, public policy or public security; the protection of health and life of humans, animals or plants”.⁵³

Concerning the TFEU provisions, it is perfectly valid to argue that public interest exceptions to internal market provisions can be invoked as an ‘overriding public interest’ in the present debate on clinical trial data disclosure; after all, public knowledge on the full effect of medicines contributes to their rational use and the protection of public health.⁵⁴

However, it is important to note that, in line with the findings of the European Ombudsman, EMA and European regulators have made it clear that clinical trial data is not to be considered commercially confidential.^{55 56}

Public access to clinical trial data protects public health

Beyond doubt, public disclosure of clinical trial data reinforces the protection of public health. Many adverse drug reactions, including deaths, caused by rosiglitazone (Avandia®) and the anti-arthritic medicine rofecoxib (Vioxx®) could have been avoided, had the public known about the undisclosed effects of these medicines. In particular, Avandia has been associated with a significant increase in the risk of heart attacks and cardiovascular deaths.^{57 58} The use of Vioxx led to an estimated 100,000 heart attacks in the U.S. alone and 10,000 deaths.⁵⁹

In spite of this evidence, the President and CEO of the Pharmaceutical Research and Manufacturers of America (PhRMA), the pharmaceutical industry association in the US, has stated that the disclosure of clinical trial data “risks damaging both public health and patient welfare”.^{xvii} In addition, a representative of AbbVie asserted that some data on adverse drug reactions should be treated as commercially confidential.⁶⁰ In actual fact, it is the *withholding* of clinical study reports that pose the greater risk to public health compared to non-disclosure.

^{xv} In light of the objectives pursued in Regulation 1049/2001, the exception to document disclosure based on commercial confidentiality has to be interpreted and applied restrictively.

^{xvi} The cornerstones of the single market are often said to be the “four freedoms” – the free movement of people, goods, services and capital. See TFEU Article 26 (2).

^{xvii} Statement made by Castellani J, CEO Pharmaceutical Research and Manufacturers of America (PhRMA) at the U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Commerce, Manufacturing, and Trade (July 24, 2013) at <http://tacd-ip.org/archives/date/2013/08>

The European Ombudsman: disclosure of CSRs and trial protocols does not undermine commercial interests

During the Ombudsman’s examination of the Nordic Cochrane Centre vs EMA case, the Ombudsman concluded that the requested clinical trial data:

- Did not contain information that could be classified as a trade secret (i.e. formulae, manufacturing or control processes)
- Did not fall into the definition of commercial confidences i.e. “every piece of information which does not have a commercial value as such, but its disclosure might provoke damage to the party (e.g. the structures and development plans of a company, marketing strategies, etc.),
- Did not contain information on the composition of the medicinal products subject to the clinical studies, or other related key information.

The Ombudsman noted that the two concerned medicines had been patented before an application for marketing authorisation was made to the EMA (*which indicates that IP-related information was already publicly available and could not be commercially confidential*).

European Ombudsman. *Decision of the European Ombudsman closing his inquiry into complaint 2560/2007/BEH against the European Medicines Agency* (November 24, 2010).

Granting full access to clinical trial data is crucial for evidence-based medicine. When data is disclosed, independent researchers can undertake rigorous systematic reviews that can contribute to enhancing knowledge on the safety and efficacy of medicines. As argued above, a complete and accurate understanding of medicines' safety profile is crucial in preventing harm. It is equally important to allow for comparative analyses of therapies and re-analysis of medicines' claimed efficacy. Indeed, ineffective medicines can lead to harm to those patients that require them to treat a condition.⁶¹

Open access to trial data will improve cost-effectiveness of public spending

Lack of access to trial data may lead to public health resources being spent on ineffective therapies. For example, in Europe and elsewhere, large sums of taxpayer's money has been spent on stockpiling oseltamivir (Tamiflu®), an expensive flu medicine, despite its apparent lack of effect on reducing serious complications (such as pneumonia). A more comprehensive understanding of oseltamivir's efficacy resulted from an independent review update based on the evaluation of CSRs rather than published papers.⁶² It is important to note that national public health authorities take into account the outcomes of Health Technology Assessments (HTA) for decisions on the reimbursement of medicines. As such, it is vital that HTA agencies also have access to full clinical trial data for reliable assessments of the properties, effect and impact of pharmaceutical therapies.

The transparency of clinical trial data is an ethical obligation

Data transparency is also important from an ethical perspective. First, it would avoid the repetition of clinical trials of harmful medicinal products on human subjects. Secondly, if trial data is not accessible to serve public health objectives, it is an affront to the potentially large number of clinical trial participants who have undertaken risks, in order to make a contribution to improving medical knowledge. The Declaration of Helsinki, on ethical principles for medical research involving human subjects, states that authors have the duty to make publicly available the results of their studies; whether positive, negative, or inconclusive.⁶³ Indeed, data secrecy is unethical because it "goes against the fundamental principles of science: we rely on transparency about methods and results, so that every experiment can be double checked and critically appraised."⁶⁴

Disclosing clinical trial data: the way forward

The current situation of limited access to clinical trial data impedes evidence-based medicine and leads to an increased use of inappropriate and/or unnecessary treatment. Hence, it is imperative that this data is publicly available for increased public knowledge on the real effects of medicines. The following policy recommendations shall be considered:

Register all clinical trials in a publicly accessible database

- Every clinical trial must be comprehensively registered in an EU-wide electronic database, that is easily accessible and available free of charge.
- Registration must be done at the point of application for approval (i.e. prior to decision). An accurate and complete record of all clinical trials submitted for approval should be maintained on the database. In addition, a list of all known clinical trials undertaken on the product being tested should be submitted by the sponsor and subsequently published.
- Under no circumstance, should patients be recruited if a trial has not been registered.
- Prior to evaluation, approval bodies have to publish the criteria by which the trial application will be evaluated.

- Ideally, clinical trial protocols should be published at the time of application but at a minimum, immediately after the approval body has made a decision (whether favourable or unfavourable). At this stage, regulatory documents, including the results of the deliberation, must also be made publicly available.
- All the above mentioned information must be published in an accurate and timely manner.

Make full clinical trial data publicly accessible

Full clinical study reports, including properly de-identified patient-level data, have to be made available in an EU-wide public electronic database, that is easily accessible and available free of charge. Ideally, clinical data from *all* trials should be made immediately publicly available following the end of the trial.

It is acknowledged that the current discussions on the Clinical Trials Regulation focus mainly on disclosing clinical data on from trials intended to be used for obtaining a marketing authorisation for the investigational medicinal product. Taking into account this particular context, the following provisions, understood as *minimum requirements* of data disclosure, should be considered.

Set preconditions for the consideration of marketing authorisation

- Regulatory bodies^{xviii} should only review applications that contain evidence of trial registration in a primary or partnered registry of the WHO International Clinical Trials Registry Platform.
- Applicants must submit the original trial protocol and any subsequent amendments, clinical study reports and the corresponding appendices to the regulators, in line with international standards (i.e. ICH E3).
- Raw data such as patient-level data have to be submitted in a computer readable format.

Publish clinical trial data submitted for marketing authorisation

- Full clinical study reports including appendices, as well as regulatory documents, must be made available on the publicly accessible database immediately after a decision on the medicinal product in question has been taken (whether positive or negative).
- In addition, regulatory bodies need to progressively publish, on the publicly available database, all data held by them from clinical trials on medicines that are already present on the market; this means medicines approved in the past 10 years (at minimum).
- Retroactive publication has to be completed in a timely manner, according to a publicly available and ambitious timeframe. While these data are not available on the database, they must be fully disclosed whenever requested.
- Regulatory bodies must request marketing authorisation holders to submit the patient-level data that have not been previously submitted in former applications.

^{xviii} The EMA for the centralised authorisation procedure and national medicines agencies for national authorisation procedures.

Set up a disclosure timeline for data that is not eventually submitted for marketing authorisation

- Whenever the sponsor has not applied for a marketing authorisation within a set timeline, it must submit the full clinical study report to the database for publication. Ideally, publication should be done within one year. Under no circumstance the deadline should exceed three years.

Ensure compliance with data disclosure

In general, when compliance with the requirements for data disclosure has not been achieved within a specific timeframe, fines or other means of punitive damages (e.g. suspension of marketing authorisation) must be applied.

Make post-authorisation safety and efficacy data publicly available

Many serious adverse drug reactions are only discovered after a medicine has been approved. Although this paper has addressed the question of access to clinical trial data, it acknowledges that it is also of utmost importance to ensure that public access is granted to post-authorisation safety and efficacy data. This includes for example periodic safety update reports (PSURs) and ADR reports.^{xix}

For more information about HAI Europe's Access to Clinical Data project, contact

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^{xix} These documents, submitted by manufacturers to regulatory authorities, provide information on new spontaneous adverse reactions and research results. Despite their safety value, these reports are often kept secret on the grounds of commercial confidentiality. In fact, an assessment of the European Ombudsman concerning a complaint lodged against the EMA for its refusal to disclose ADR reports found that the requested documents did not contain any commercial confidential information. For more information see B. Mintzes: Medication safety: opening up the black box. *BMJ Qual Saf*, 22:702-704 (2013) doi: 10.1136/bmjqs-2013-002238 and European Ombudsman *Decision of the European Ombudsman closing his inquiry into complaint 3106/2007/(TS)FOR against the European Medicines Agency* (December 14, 2011).

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