**Open Source Malaria Entry for the Cochrane REWARD Prize**

*1) Describe the initiative and how it has addressed research waste in at least one of the 5 stages of research (questions, design, conduct, publication, reporting) in the area of health*

Open Source Malaria (OSM) aims to discover and develop new medicines for the treatment of malaria through an open source research model that eliminates research secrecy and duplication of effort. The consortium operates according to a set of Six Laws, the most important of which are: i) all data and ideas are freely shared, ii) anyone may take part at any level and iii) there will be no patents.1

The consortium, founded in 2012, has operated with a modestly funded core of one full-time researcher supported by the Australian Government and an NGO (the Medicines for Malaria Venture, Geneva). This core leverages considerable in-kind contribution from the wider community: to date more than 300 people have participated in various ways, from strategic advice and technical expertise to the physical preparation and testing of drug candidates.

Four series of antimalarials have been evaluated. The first showed promise, but was parked because of (currently) insuperable roadblocks; the work was published.2 Series 2 was abandoned when it was discovered that another group was working on it, in secret. Series 3 is undergoing studies to identify its molecular mechanism of action. Series 4 has been extensively evaluated because of its exceptional promise: the constituent molecules are able to cure mice of a model of malaria. This 4th series is positioned well to achieve a world first: a molecule from an open source project entering clinical trials.

OSM reduces research waste in the following ways. Examples are provided under Question 2.

**a) Conduct.**

The most important way in which OSM reduces research waste is by avoiding unnecessary duplication of effort. Everything is in the public domain in real time, including experimental failures, inactive molecules and undesirable outcomes.

**b) Reporting.**

Transparency, via reporting research online and in real time, means that all onlookers know what everyone is doing, and if work is contributed it is because that contributor knows that that work is currently needed. The knock-on effect is that contributions may be made spontaneously by highly qualified individuals from anywhere in the world.

**c) Questions**

The direction of the research consortium is openly debated, on a democratized platform where seasoned pharmaceutical professionals are able to interact with junior students. Debate and research occur simultaneously, *allowing the community to change the research direction before it is completed*.

**d) Design**

The technical platform uses existing online infrastructure3,4 that allows for the widest number of people to participate, and builds/promotes open standards wherever possible. Future improvements are constantly being sought as part of the discussion so that others from outlying disciplines (*e.g.,* software development) can contribute.

**e) Publication**

OSM publishes its work in open access journals and other publicly accessible media in order to ensure full data availability. Research papers are openly and collaboratively written to allow authorship by anyone. The papers themselves make clear what the community can do next to advance the science quickly.

*2) Describe any (pilot) data showing how the initiative has lowered research waste.*

Further to the above, specific examples of how OSM has lowered research waste are as follows:

**a) Conduct**

All drug candidates in OSM are shared openly, along with their biological efficacy, so it is clear to everyone which molecules are worth pursuing and which are not. The data are available for use by anyone in perpetuity.

1. In 2017 in OSM Series 4, a US team independently showed that a molecular modification was deleterious, saving time and effort of other teams. A group of students in Brisbane is now modifying another atom of the molecules to see if this regains potency.
2. Student crowdsourcing has been undertaken extensively (Australia, UK, US). Research waste is reduced by students generating outputs that are used in a real-world project, rather than generic laboratory outputs that are discarded.
3. Spontaneous contributions are not limited to academia. The most promising-looking molecule in Series 4 has been contributed by a leading research group from Pfizer (USA), who are providing their time and expertise freely because they know their work will advance the science.
4. Waste is reduced by avoiding work that is being undertaken by another organization behind closed doors, as happened with OSM’s Series 2. Work ceased when it became known that another team elsewhere was looking at similar molecules, and resources were quickly reallocated.
5. OSM is decentralized. The team expands and contracts as needs arise. There is no inflexible infrastructure cost (*e.g.,* a dedicated building) and people are not contractually locked in, leading to low transaction costs.

**b) Reporting**

Open, online laboratory records kept by OSM contributors contain machine-readable strings that allow for maximal discoverability through search. The physical samples created by contributors are freely available for others to test *vs.* other pathogens, as has already happened *vs*. tuberculosis, other bacteria and fungi.

**c) Questions**

The continual peer review at the heart of OSM lowers research waste by making it less likely that unproductive research will be pursued. In Series 1, a significant debate about a potential weakness of the molecules arose after a spontaneous contribution from a leading expert. The resulting decision-making process, recorded on YouTube, led to research effort on the series being scaled back significantly. The decision saved considerable resources that would have been expended had the research not benefitted from unrestricted peer review.

**d) Design**

The technical and infrastructure needs of OSM are publicly debated. It would be efficient for the platform to “perceive” the molecule a scientist is working on and automatically connect that person to other scientists working on that same molecule. This need was discussed, planned and published so it may serve as a proposal for funds.5

**e) Publication**

The paper describing Series 1 was published alongside compressed versions of all laboratory notebooks that can be browsed, searched and reused. The current writing of a paper on Series 4 allows federated contributions from everyone and employs Github as a public filesharing system.6 This increases efficiency by allowing continual peer review during writing.

*3) Describe how the initiative might potentially be scaled up*

a) *A Broader Movement*. OSM has contributed significant evidence that there is major social enthusiasm and support for approaches to new medicines that are transparent and distributed. Scale-up requires more funding of the project core, which will allow more contributions from the community to be folded in to a unified project output.

Greater core funding requires clarity on the economics of how an open source medicine can make it to market. To achieve this clarity, a broader *open source pharma* movement has been created (of which OSM is a part) to refine alternative business models that can compete with the traditional pharmaceutical industry.7

With increased core funding comes a more efficient marshaling of community resources through a matrix of mentors and mentees. Such systems have precedence in software development, where core industry funding has led to large-scale open source community projects delivering market-leading products (*e.g.,* Google’s Chrome browser).

The structure of OSM may be easily applied to other diseases, as has recently occurred with the deployment of related tools to the neglected tropical disease mycetoma.8

b) *Welcoming of Others*. OSM is covered by the Creative Commons CC-BY license, meaning everything it generates may be used by anyone for any purpose, including to make money, provided the consortium is cited. This retains the widest possible use and discoverability of the research while allowing a commercial body to take a discovery through to market if that is the most cost-effective way to help patients.

4) *Provide a justified estimate of the potential reduction in research waste that the initiative might achieve.*

The greatest cost in the development of new medicines is failure. A powerful exemplar of how OSM reduces research waste would arise if an open source series failed in development. Lessons would be learned by all onlookers about the failure and how it could be avoided by related series of molecules in the future. If OSM led to one such series failing late in an antimalarial drug development program (which overall costs roughly $200M or $30M with/without factoring attrition9), this would save others *ca*. $50M, depending on the timing and nature of the failure.

Related to this are open source drug development programs that are “parked” and then archived, awaiting resumption by others. All project data are in the public domain, including far more detail than is ever found in a traditional academic publication. Series may be resumed, or added to, by anyone as though they were project insiders. This avoids future scientists needing to repeat the research of others. Such open repositories of projects from the pharma industry would have great value, particularly where the pharma companies have closed due to financial pressures and suffered enormous losses of intellectual capital (*e.g.,* the AstraZeneca closure in Bangalore). Retaining one pharma series fully in the public domain would save others repetition costs of *ca*. $5M per Late Lead candidate.

Most of the research waste that is avoided, however, is challenging to quantify because it is highly granular, with many small savings across a spectrum of projects over long periods of time: avoiding duplication, drawing in highly skilled individuals and sharing resources.

**References**

1) Open Source Malaria: opensourcemalaria.org, accessed May 11th 2018.

2) Open Source Drug Discovery: Highly Potent Antimalarial Compounds Derived from the Tres Cantos Arylpyrroles, A. E. Williamson, et al. *ACS Cent. Sci.* **2016**, *2*, 687–701. DOI: 10.1021/acscentsci.6b00086

3) Experiences with LabTrove, a Researcher-centric ELN, K. A. Badiola et al. *Chem. Sci.* **2015**, *6*, 1614-1629. DOI: 10.1039/C4SC02128B

4) Open Source Drug Discovery – A Limited Tutorial, M. N. Robertson et al. *Parasitology* **2014**, *141*, 148-157. DOI: 10.1017/S0031182013001121

5) SCINDR - The SCience INtroDuction Robot that will Connect Open Scientists, C. Smith, M. H. Todd, L. Patiny, C. Swain, C. Southan, A. E. Williamson and A. Clark, *Research Ideas and Outcomes* **2016**, 2:e9995. DOI: 10.3897/rio.2.e9995

6) For example: the Github repository for OSM Series 4: https://github.com/OpenSourceMalaria/Series4 (accessed May 11th 2018).

7) An Open Source Pharma Roadmap, M. Balasegaram, P. Kolb, J. McKew, J. Menon, P. Olliaro, T. Sablinski, Z. Thomas, M. H. Todd, E. Torreele and J. Wilbanks, *PLoS Med.* **2017**, 14(4): e1002276. DOI: 10.1371/journal.pmed.1002276

8) New Open Source Drug Discovery Project Aims to Develop Mycetoma Treatment, https://www.dndi.org/2018/media-centre/press-releases/new-open-source-drug-discovery-project-develop-mycetoma-treatment/ (accessed May 11th 2018).

9) From Pipeline to Product: Malaria R&D Funding Needs into the Next Decade, PolicyCures, http://policycures.org/downloads/From%20Pipeline%20to%20Product%20full%20report.pdf (accessed May 11th 2018)

**Supporting Items**

1. Article in The Conversation (Sept 14th 2016) entitled “*Making drug development less secretive could lead to quicker, cheaper therapies*” by Professor Todd and Dr Alice Williamson, accompanying the publication of OSM’s first paper (PDF attached).
2. Video of Conference Presentation at Linux.conf.au (January 2018) by Professor Todd entitled “Open Source Pharma” about the Open Source Malaria consortium: <https://www.youtube.com/watch?v=VBodnd68iwU>
3. Article in the Guardian (19th April 2017) entitled “Why Open Source Pharma is the Path to Both New and Cheaper Medicines”
4. Article in the Guardian (1st Dec 2016) detailing the use of OSM in a crowdsourced project in which school students made samples of the expensive drug, Daraprim