Q & A – Day 1 Tuesday 25 August 2020

Free Live WC11 webinars on 3Rs in COVID-19 research
25 and 26 August 2020 | 3 PM CET

Please find below an overview of the questions and answers for day 1 of the webinar series.

PENNY HAWKINS

Name: Daniel Simonsen

- Are there any case studies of research not conforming to current legislation and regulations and overlooking the use of animal-free methods in Covid-19 research? Or case studies of research not properly implementing the 3Rs due to the 'covidisation' of research?

  I based these concerns about the 'scramble' to use animals on two issues. The first is the current reproducibility crisis across all life sciences, and the second is the many deep concerns that have been expressed about the quality of clinical COVID-19-related research (I cited a selection of these in the presentation). If this is happening in clinical research, it is likely also a risk within in vivo projects. Poorly designed, executed and reported animal experiments have been getting past multiple gatekeepers for years now, including local committees, regulators, funding bodies and journal editors. A number of initiatives are tackling this problem (see https://www.nature.com/articles/s41562-016-0021, https://norecopa.no/prepare, https://arriveguidelines.org/) but there are still serious issues with experimental design and refinements are not always implemented. There is currently a lack of training in good experimental design, and apparently poor understanding of the consequences if design is flawed - and this is unfortunately mirrored with respect to all 3Rs. Expertise in searching for, and identifying, alternatives is lacking, as are incentives to replace animals. 'Desperation science' is sadly likely to make matters worse, which would have negative consequences for human patients as well as lab animals.

Name: Samantha Saunders

- Based on your comments about not knowing which approach will contribute the most to scientific progress and measuring impact in real world terms rather than publications, do you think that a retrospective review of COVID-19 research in two or three years' time would be useful? Do the RSPCA plan to do anything like this?

  Yes, retrospective reviews would be absolutely essential, not least because further pandemics are pretty much inevitable unless significant changes are made to some human uses, and abuses, of animals. A globally coordinated retrospective review would enable an evaluation of the relative contributions and value of all the approaches currently in use; those animal 'models' that are most in need of replacement could also be identified and efforts coordinated to achieve this. The RSPCA wouldn't have the resource to undertake a review on such a scale, but I would hope that reviews will be carried out by research funders and regulators such as the European Commission: https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/coronavirus-research-and-innovation/financing-innovation_en

Name: Jan Turner

- How can we practically incentivize AWBs/IACUCs to look for and implement 3Rs? And how can we practically measure scientific impact of research by clinical outcome rather than based on publications?

  In the case of Animal Welfare Bodies, this is a fundamental part of their role – see Directive

  Article 27 (1b) and page 7 of the European Commission Working Document on the AWB (https://ec.europa.eu/environment/chemicals/lab_animals/pdf/endorsed_awb-nc.pdf). Page 10 of the Working Document emphasises that the AWB should have an appropriate level of authority, and terms of reference that are endorsed and visibly supported by management. There's a very helpful section on delivering the tasks of the AWB, including advising on the application of the 3Rs, on pages 10 to 15. If an AWB is not delivering this task as set out in the Working Document, and is not properly supported by senior management, there is something wrong and AWB members need to ask the person responsible for ensuring compliance with the Directive to take remedial action.

  Many universities are assessing their research impact beyond numbers of publications – if you type 'research impact' into a search engine you will find many establishments' web pages listing case studies and examples. In the UK, ResearchFish (https://researchfish.com/researchfish/) was set up by the Research Councils to collect information on the research activities of their award holders. Principal Investigators have to submit information about the outputs, outcomes and impact of their research. This could be done more widely and is critically important for accountability, given that the public (directly or indirectly) funds research, and it is done in the public's name.

CHRISTIAN DESAINTES

Name: Roberta Staley

- Please explain how the drug for osteoporosis came to be identified as a possible Covid-19 drug.

ALL

Name: Daniel Simonsen

- Is the example of vaccine development skipping pre-clinical animal trials and going straight to human trials an example of the negatives impacts of the Covidisation of research, or positive?

  Penny Hawkins: Assuming that the preclinical trials would be skipped because they were not necessary (because they did not yield useful data and/or they could be replaced by Non-Animal Technologies), this would be a positive aspect of the 'Covidisation' of research. This is

because it would represent a step towards making medical progress whilst also replacing animals and avoiding their use and suffering.

Koert Stittelaar: I think this example should just be seen as a rapid outbreak response and can only be applied if the concerning vaccine platform is already extensively tested in earlier trials; What you see is that still vaccine safety and efficacy animal studies are required by authorities.

Name: Kathrin Herrmann

- Why do we still talk about 'alternatives' (to the 'gold standard' of using non-human models) when we should be talking about human biology-based and thus human-relevant research?

Penny Hawkins: I agree with the thinking behind this question – a 'model' should not be taken as a Gold Standard if a study is aiming to understand human biology, or address a human medical problem.

Koert Stittelaar: Because efficacy testing of vaccines, especially dose directed against highly pathogenic (classified as BSL-3), cannot be performed in humans at the moment until 'alternatives' are fully validated.

Name: Martje Fentener van Vlissingen

- What cell models for SARS-CoV-2 infection also model for inflammatory responses?

Koert Stittelaar: In principle most of the human-based cell models can be used at least for a defined aspect of the inflammatory system. Obviously, human primary epithelial cultures, human organoids and organs-on-a-chip are closest to the primary cell types and there are possibilities to add additional components of the (innate and adaptive) inflammatory system like NK cells and antibody

Name: Jie-Long He

- As we know, COVID-19 research is very urgent for us. We should choose the traditional animal experiment or novel alternative methods? Have any risk? How to assess risk? Thanks!

Penny Hawkins: From an ethical standpoint, it will always be desirable to replace animal experiments with Non-Animal Technologies. In the UK and European Union (EU), the legislation regulating animal use presumes against animal experiments and requires the use of humane alternatives wherever possible. The key phrases in the EU Directive are 'wherever possible' and 'scientifically satisfactory', both of which may call for judgements about risk. Identifying and assessing risks for alternatives in coronavirus-related research is not my field, so I hope my fellow speakers can help to answer that aspect …

Koert Stittelaar: An enormous number of people is waiting for a safe and effective vaccine, risks must be avoided or at least brought to a minimum, and we do have the obligation to use alternatives if possible and available . Concerns about vaccine safety in the community could lead to a discouragement of vaccine use and that could lead to a too low vaccination

coverage and the virus to continue to circulate.

Name: Sandra Coecke

- Regarding vaccine therapy, phage display is embracing progress in science and technology. Some of the vaccines that are developer use the technology. What can be' done as a community to prioritise such vaccines once there safety has been proven to move to a drive approach and also use the vestibilità of such vaccines to be' prepared more quickly to future virus treats.

  Koert Stittelaar: Phage display is one of the important platforms for active and passive immunization strategies, but the safety and efficacy testing needs is in principle similar as for other platforms

Name: Tom Masding

- As we move towards a world with greater use of alternatives. What advice do you have to the younger viewers who are starting university or first job. How can they make concrete efforts to contribute?

  Penny Hawkins: Make sure that you receive proper training in searching for alternatives in your specific field – there is unfortunately no one-stop shop and you will need to acquire appropriate expertise. If there is an Animal Welfare Body, Institutional Animal Care and Use Committee or equivalent at your place of work, engage with this, ask it for help and support its initiatives. Keep up with developments in the field via centres of excellence such as the Wyss Institute https://wyss.harvard.edu/) and CAAT (https://caat.jhsph.edu/about/_includes/index_eu.html) and also keep up with reports on Non-Animal Technologies by bodies such as the European Commission (https://ec.europa.eu/environment/chemicals/lab_animals/3r/pdf/scientific_conference/non_animal_approaches_conference_report.pdf). Seek out helpful contacts and mentors – hopefully you will be able to do this at a face-to-face World Congress in 2021 …

Name: Paulin Jirkof

- How important do you think animal research is for COVID 19 research (given the fact that only such a small part of the EU budget is invested in animal experiments)?

- What refinements can you apply to reduce burden / increase welfare in the ferret / rabbit infection experiments? (other than humane endpoints)

  Penny Hawkins: I don't have specific expertise in this field, but you could try the Norecopa database: https://norecopa.no/

- Many people use the pandemic as an argument for the need of animal research and against initiatives to replace/reduce animal use, how do you feel about this trend?

  Penny Hawkins: Researchers are using a range of approaches in the search for vaccines and treatments for COVID-19, including epidemiology, computer modelling, clinical research,

clinical trials, Non-Animal Technologies and animal models. Nobody can predict the extent to which each of these will contribute to any given vaccine or therapy, and any argument for the necessity of one of these could be applied to all of them. I personally find it distasteful to politicise this desperate situation and use it as an argument to promote animal research in general.

Anne-Dominique Degryse

- Are there data showing that rabbits or hamsters got infected by COVID infected people (kids...)?

- What make you choose the 3 animal species used in testing Corona e.g rabbit? and the route vs species?

Name: Ryan Waters

- What was your scientific objective(s) you used to define a 'successful model' of COVID19 infection?

  Penny Hawkins: One criterion for a 'successful model' would be whether it had genuine impact in helping to bring a new medicine, vaccine or medical device to the clinic. This obviously requires retrospective reviews, which are especially important in the case of animal 'models' that cause pain, suffering, distress or lasting harm, to evaluate whether the proposed benefits were realised.

Name: Bea Zoer

- Are there examples of cases in which the ethical evaluation has been less critical to support fast start of COVID-19 animal research? Does that also apply to clinical studies? Thanks!

  Penny Hawkins: COVID-19 has provided a real test for the ethical frameworks that are used to make decisions about the justification for research projects that use animals. The concerns that have been expressed about the rigour of clinical studies, by multiple commentators, indicate that some processes have not been sufficiently robust to stop poorly designed and conducted research from being funded and reported (see my slides). If this is happening with research involving human subjects, it is likely a risk for in vivo projects too. However, it is not inevitable if the harm-benefit analysis is properly applied, and I know that many regulators, ethics committees and members of the scientific community are mindful of this