Oxford’s PRINCIPLE Trial: Bringing Ivermectin Directly into the Developed World in the Battle Against COVID-19

By TrialSite Staff January 25, 2021

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The University of Oxford soon kicks “the PRINCIPLE Trial” into a higher gear now, in what they consider a pathbreaking “high-quality trial” of Ivermectin, a generic drug already evidencing significant efficacy in over two dozen clinical trials around the world, according to some researchers. The UK government also backs this pivotal study via the Department of Health and Social Care. Searching for early-onset, home-based ambulatory treatments for COVID-19, the PRINCIPLE Trial seeks to meet a gap in research in the world’s richest nations to date. Nearly all of the taxpayer-financed research-based expenditures of governments in the US, UK and Europe, for example, have gone into vaccines, novel monoclonal antibodies, and novel therapeutics, with an emphasis on treating severely ill patients. Ivermectin, hailed as the “wonder drug” or “the People’s medicine” for COVID-19, gains growing attention worldwide made more widely available, frankly, partly due to TrialSite’s consistent chronicling of these trials around the world since the original University of Monash breakthrough. The team discovered that in a lab cell culture, Ivermectin obliterates the novel coronavirus within 48 hours. Since then, TrialSite has covered most studies worldwide, whereas, by the summer, groups in the U.S., such as the Front Line COVID-19 Critical Care Alliance (FLCCC), commenced meta-analysis covering the dozens of Ivermectin studies around the world. According to these physician/scientists, the results reveal compelling data that Ivermectin actually reduces the COVID-19 death rate while accelerating viral clearance and transmission reduction. Enter the preeminent University of Oxford and the PRINCIPLE Trial: the globe’s top investigators now seek to finally test if Ivermectin and antiviral Favipiravir, both low-cost, orally-administered, generally available generic drugs, can be proven safe and effective in a “properly designed trial.” Led by Co-Chief investigator Chris Butler, Professor of Primary Care, Nuffield Department of Primary Care, Health Services at Oxford, the study team is generally upbeat about the prospects. Still, Dr. Butler notes the “gap in the data.” A critically important trial, the PRINCIPLE Trial, is also causing a stir. Groups such as the FLCCC raise the Helsinki Accords: from their vantage, they remind all about the question of ethical conduct—is it right and proper to conduct a randomized placebo-controlled trial when there is sufficient evidence that a drug can save lives? Couldn’t a dose control study or well-designed observational study be run instead to both generate data and protect patients? On the other hand, that Oxford is the first major center to embrace this important generic drug is truly game-changing and demonstrates the leadership position of that research institution again.

‘Not a Great Place to be’

New York, New York: For Second Time Doctors and Patients Need to Go to Court to Access Ivermectin

and a number of funding governments use of taxpayer money. In the U.S., for example, Operation Warp Speed, in conjunction with the NIH's ACTIV, has spent over $13 billion of taxpayer money on just a handful of vaccine and novel monoclonal antibody developers, yet the nation has experienced a staggering amount of death from the pandemic.

A growing cry by physicians and other medical professionals for drugs that can be used at the early onset of the virus, to impede the progression of infectious severity, hasn't been reflected in the research spent to date.

But other nations have commenced with programs to treat early-onset treatments with antivirals or Ivermectin. Albeit, these tend to be low-to-middle-income countries (LMICs) with far fewer resources than would be available in America, Britain or Europe, for that matter. These poorer countries must be ever more resourceful—they don't have many billions of dollars to spend during a pandemic on lengthy, randomized, placebo-controlled studies.

Russia led a series of agile studies that led to the approval of Favipiravir, as has India (with multiple generic versions), and several other countries. Ivermectin is used in India's state of Uttar Pradesh, with 210 million people, health officials there swear by the results. The same is occurring in some Brazilian states, Bangladesh, and for that matter, Peru and Argentina. TrialSite commissioned a documentary about this unfolding situation in Peru. In Europe, at least in the south eastern fringe, the use of Ivermectin gains steam in Greece and the Balkan Peninsula.

Frustration Enters the "First World"

But the "First World" that is the wealthiest Western nations have experienced some of the most horrific losses from this pandemic. The U.S. has been the epicenter of the pandemic, with over 400,000 deaths.

The Times' Blakely spoke with Wellcome Trust's Nick Cammack, who shared that there are only "…two strong new antiviral candidates in the pipeline to date. One is called molunpiravir (EIDD-2801) from Merck." Taken via tablet form and reported on by TrialSite, it is apparently designed to actually "…interfere with an enzyme that the virus relies on to replicate." Cammack shares that if the clinical trials perform, the drug could be available toward Q3 2021.

Dr. Cammack also introduced Roche's AT-527, another antiviral drug that is early in the pipeline. This gap, Cammack frets is, "… worrying." That is, "To have only a few potential therapeutics for a nasty disease during a global pandemic—it's not a great place to be. We need a big push in R&D."

In the United States, *TrialSite* was one of the only media at the time to report on the breakthrough findings of the ICON study in Broward County, Florida. There, Dr. Jean-Jacques Rajter and the team from Broward Health discovered amazing results from the ICON observational study, which evidenced, among other things, that Ivermectin could lower the COVID-19 death rate. The results were finally published in CHEST, but they were not considered strong enough as ICON was observational and not a randomized, placebo controlled study.

Many doctors in the U.S. started prescribing off-label, and with every trial result that TrialSite reported on, the data gained strength. There was some mounting evidence that Ivermectin definitely could inhibit the coronavirus. TrialSite for months called out for NIH funding of Ivermectin studies: the online media platform's founder even wrote an urgent email communication to NIH Director Francis Collins.

Enter Oxford's PRINCIPLE Trial

Perhaps there is no stronger brand in research than that of Oxford University. One of the world's most renowned investigational hubs, this prominent group, led by Dr. Peter Horby, conducted the RECOVERY trial, which showcased and found the benefits of corticosteroids in more severe COVID-19 cases. Backed by the UK government, now The PRINCIPLE Trial seeks to confirm whether low-cost, easy-to-administer drugs such as Ivermectin and Favipiravir can truly inhibit the coronavirus.

In the recent *The Times* article, journalist Rhys Blakely interviewed Co-Lead investigator Dr. Butler who acknowledged that Ivermectin "… Has potential antiviral properties and anti-inflammatory properties, and there have been quite a few smaller trials conducted in low-and-middle-income countries, showing that it speeds recovery, reduces inflammation and reduces hospitalization…"

"The Data Cop"

According to this group, the existing data leads to a clear-cut case of evidence for A.) additional dosing studies and B.) emergency use authorization as lives need to be saved now. Already, over 400,000 lives in the U.S. have been lost, despite over $13 billion in taxpayer-supported major clinical trials, primarily targeting vaccines and novel monoclonal antibodies.

But this isn't enough for what is considered by the biomedical research establishment, including the prominent University of Oxford. The studies in places like Bangladesh and Columbia; Egypt and Argentina; Iraq and India; and Mexico and other LMICs aren't sufficient. Be it flawed, study design, too much dosing variability, or not sufficient numbers of patients, the evidence must be established elsewhere. That significant groups in America and Britain have studied these underlying studies, and assembled meta-analyses pointing to strong data for efficacy isn't good enough for the apex research institutes and the West's major academic medical centers.

While some groups such as the FLCCC call for immediate emergency use authorization and dose-finding studies, the major research center scientists and principal investigators, as well as health authorities, still see a gap in the data that must be filled.

As expressed by Dr. Butler with Oxford "…There's a gap in the data. There's not been a really rigorous trial."

For that matter, neither does Rockstar Principal Investigator Peter Horby, also with Oxford. Dr. Horby led the RECOVERY trial, proving that dexamethasone could reduce COVID-19 death rates, at least in severe scenarios. According to this world-renowned principal investigator, the data covered in the meta-analyses was "interesting, perhaps encouraging, but not yet convincing," reported Blakely with *The Times*.

The Study

First, *TrialSite* commends University of Oxford, the British government and Dr. Butler for progressing this study. No matter the critique that follows, Oxford and the Butler study team were the first to declare the intention to take on this mission-critical effort among the highly industrialized nations of the "West." That the PRINCIPLE Trial's leadership embrace both Ivermectin and Favipiravir is a big deal.

In a quest to finally establish safety and efficacy for a low-cost drug that can work earlier–that is, right when COVID-19 symptoms appear, Professor Butler and team seek to establish if Ivermectin can prevent viral replication, thus stopping the SARS-COV-2 pathogen from entering the human host, reports *The Times*.

Called The PRINCIPLE Trial (ISRCTN86534580), study details can be found here.

The study will employ a number of channels to recruit patients, from GPs and online to contact-tracing systems in Britain to find patients that are either A.) 65 and up or B.) 50 and up, experiencing health conditions that could pose a greater risk.

Study Flaw?

The Times reports that some experts such as Penny Ward, visiting professor in pharmaceutical medicine at Kings' College London critiques the study, sharing with *The Times*' Rhys Blakely that, "They're allowing a recruitment window 14 days from the onset of symptoms, but the virus peaks on day three—and it's too late to use an antiviral after the peak of virus replication."

Dr. Ward continued for The Times, "And if you don't intervene very rapidly with an antiviral, you will have a failed trial—even though the drug itself might, in fact, have been effective if given correctly. If they do get the skates on and get patients into those trials within two or three days of the first onset of symptoms, then there's a fighting chance that one or two of those might actually be effective."

Ethics of this Study Questioned by Some?

On Saturday *TrialSite* interviewed the head of the FLCCC Dr. Pierre Kory on their position on this study. He shared that although they were pleased that *The Times* reporter considered their point of view, their full quotes from Dr. Paul E. Marik were precluded from the article.

The FLCCC is adamant about the need for more Ivermectin research; however, based on the principles of the Declaration of Helsinki, Kory articulates, "it's unethical to use a placebo-based study when the evidence is clear that a medicine actually works." Because that means that people can become more ill and even die with the foreknowledge that the medicine could be used to save those very lives.

In the interview, Dr. Kory was very clear that the evidence favors immediate emergency use of Ivermectin at least, and that any study should be designed as a dose-finding study, for example, and well-designed observational study establishing the anti-parasite medicine as standard of care, measuring the differing outcomes utilizing sophisticated propensity matching and access to Big Data for full

Why do Dr. Butler, Dr. Horby and so many other scientists and researchers not accept the evidence that's been generated to date? It comes down to a few key factors such as the following:

- The present studies don't include enough patients
- They are not well-designed trials
- Variability in dosing in the studies

In regard to the number of patients, Kory noted that at least 2,000 patients are now covered by the meta-analyses created in both America and the UK. He shared that a meta-analysis—that is, an analysis of many underlying Ivermectin-based COVID-19 clinical trials—represents the strongest form of evidence.

He pointed out that the meta-analysis is stronger than any single underlying trial. The FLCCC's reading of their meta-analysis of Ivermectin studies is clear: the low-cost medicine has a significant impact on mortality, viral clearance and viral transmission.

But what about the critique that these studies from LMIC's are not "well designed?" For example, the dosage amounts vary across the dozens of studies. Dr. Kory shared this critique is strange, if not senseless. He pointed out that dosage variability schemes are actually good; they evidence differing forms of efficacy and actually contribute to the quest for the ultimate dosing strategy. Kory suggested compelling research at this point would be a dose-finding study.

Okay, on to the critique that the underlying LMIC-based studies were not well designed? Some of the Ivermectin studies, critics point out, were open-label, leading to possible bias.

That these studies could be influenced by subjective bias because some of them were open-label, for example? Kory acknowledged that open-label studies could lead to bias and hence, influence subjective outcomes. But he hammered on the point that the objective outcomes identified cannot be influenced by this kind of bias—that is, the actual reduction in mortality rate, viral clearance and the like are objective measures regardless.

Heavy Burden

Because the FLCCC physicians are convinced the meta-analyses research from both sides of the Atlantic points to a clear case of efficacy, they worry about the control group patients. As the group maintains that the existing evidence for Ivermectin is overwhelmingly indicative that the medicine is highly effective in reducing hospitalization, inhibiting transmission and lowering COVID-19 death rates as well as accelerating viral clearance, they cannot morally support a placebo-controlled study at this point.

They believe it's a mistake and that the Oxford PRINCIPLE Trial should be designed as a dose-finding study and/or sophisticated observational study. Kory told *TrialSite*, "It is grossly unethical to enroll patients in a placebo-controlled trial. Such a study will lead to harm to the control group." What he means is that from their perspective, because the drug is known to work, purposely not giving the control group that drug brings a heavy burden on those funding and designing the study.

Conclusion

TrialSite has emerged as a prominent objective, unbiased online daily for clinical trials, emphasizing transparency, accessibility and a focus on the trial site organization (that is, the investigational site at the hospital, clinic or commercial center).

With the aim of advancing biomedical research, TrialSite has led all media in identifying and tracking Ivermectin studies during the pandemic. TrialSite isn't a scientific journal, nor does it exist to promote one opinion or perspective. Nor is it an authority on what is evidence. It's merely a daily online news channel for those interested in research. The goal is to identify, track and monitor research, with the aim of helping empower more health care consumers, physicians and healthcare professionals with daily updates to research.

Consequently, *TrialSite* cannot opine on whether the PRINCIPLE Trial is ethical or not. TrialSite commends Dr. Butler, University of Oxford, and the UK government for funding this important research endeavor. It's the very first major clinical trial in the G8, for example, to embrace Ivermectin. As mentioned previously, a *TrialSite* founder sent an urgent request letter to the NIH, only to receive no response.

On the other hand, the FLCCC is too commended by TrialSie for their commitment, dedication, and passion to saving lives during this pandemic. FLCCC members are putting their careers on the line for the mission-critical cause of saving lives during this pandemic, which has already taken over 400,000 in America and over 2.1 million deaths worldwide.

Call to Action: TrialSite follows studies across many different therapeutic areas. Have any requests? Contact us.

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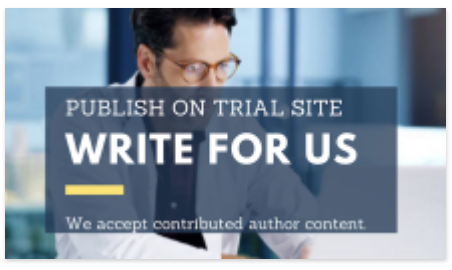

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donaldmau123 1 week ago

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people treated with ivermectin are still PCR positive and the virus gets in the brain pretty quickly. Ivermectin does not get in the brain.

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John Hainaut 6 days ago

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Have you seen how bad the Oxford Recovery trial for HCQ was. The design gave patients 6 times the maximum safe dose. This study will need very close examination.

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