UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

DATA AND STATISTICS AS A BASIS FOR DECISION MAKING

A discussion of the Corona pandemic

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DAGSTAT

- **German Consortium in Statistics**
  - Association of 13 professional / scientific societies in statistics and DESTATIS, the Federal Statistical Office, in Germany
- **Activities** include
  - Conference every three years, next DAGStat 2022 in Hamburg https://www.dagstat2022.uni-hamburg.de/
  - Symposia aiming at the public
  - White papers on topics of current interest
- **Homepage** https://www.dagstat.de/

DAGSTAT WHITEPAPERS

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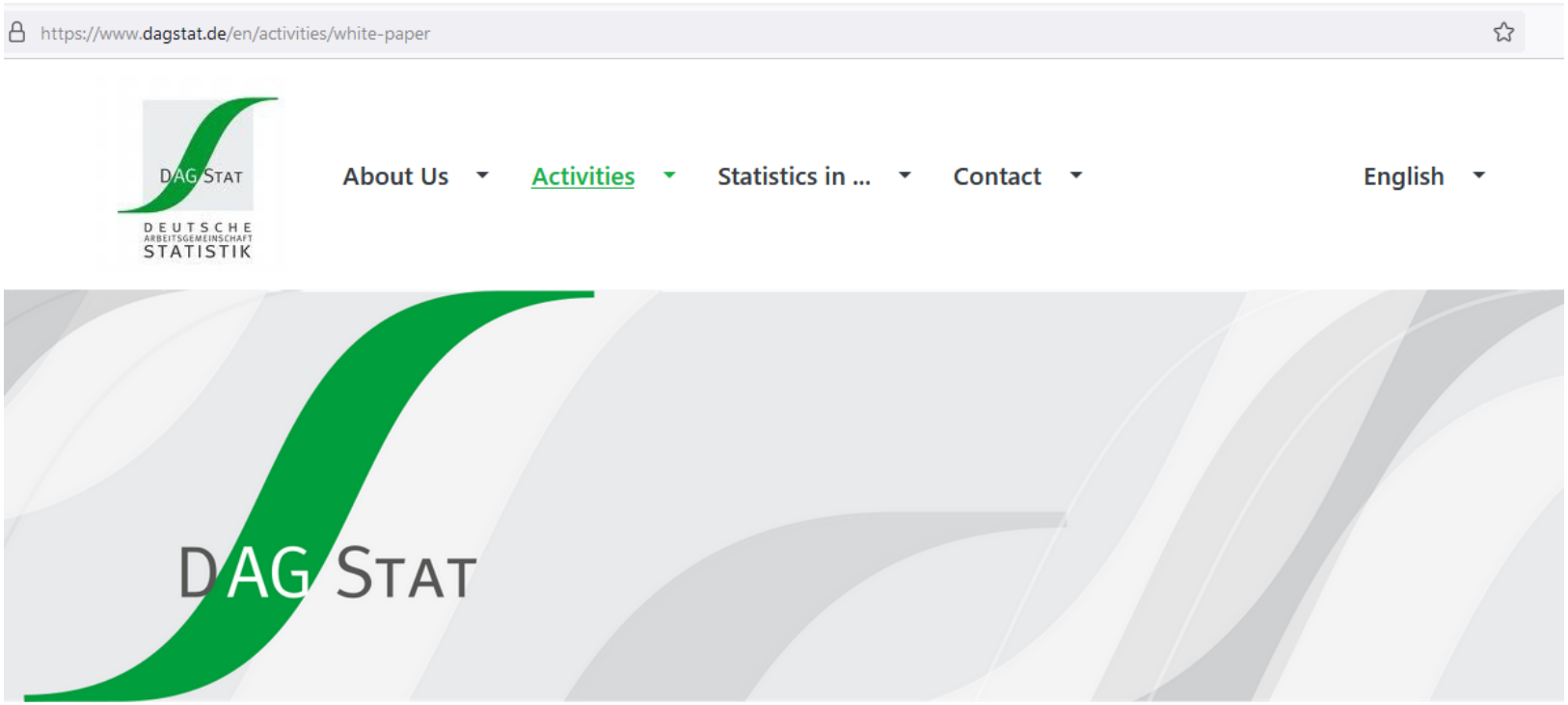

Friedrich et al (2021) Is there a role for statistics in artificial intelligence? ADAC (in press)

DATA AND STATISTICS AS BASIS FOR DECISION MAKING

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

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- Manuscript (in English) in preparation (Jahn et al, 2021)

FROM DATA TO DECISIONS

- Data: relevance, quality, availability
- Modelling: from data to insights
- Reporting and communication
- Decisions: Methods in health sciences and political decisions

DATA

- Suitability for a target / relevance
- Transparence / quality standards / truthfulness
- Sources of error
- Timeliness and accuracy (trade-off)
- Access to data for science

Fig. 3 Data relevancy and quality are equivalent components of a fit-for-purpose real-world data set. Figure according to Duke-Margolis (Duke-Margolis, 2018)

Figure 3 from: Friedrich et al (2021) ADAC (in press)

SECONDARY DATA

- Points above refer mainly to primary data generating process
- Data from available sources considered with data generation different from aims of current study, e.g. number of infections reported by local health authorities used for comparisons between regions
- Potentials issues include selection bias, informative sampling
- Risks may be mitigated by additional data such as number of tests and reasons for testing in the example above
- Representative samples (regional granularity, time scale)

MODELLING: FROM DATA TO INSIGHTS

- **Mathematical representation** of data generation (assumptions)
  - Stochastic and non-stochastic
- **Purposes of modelling**
  - Understanding / explanation
  - Estimation (e.g. R value) / prediction (e.g. ICU capacities): e.g. statistical models, agent-based models
  - Decision analysis (e.g. evaluating / ranking alternative interventions): e.g. agent-based models
- Assessment of **uncertainty** and **causality:** Importance varies with the purpose

METHODS FOR DECISION MAKING

- **Decision analysis** (also called decision-analytic modelling)
  - Often based on computer simulations
  - Decision-analytic framework includes health states, events describing possible disease trajectories, type of analysis, simulation method
  - Scenario and sensitivity analyses
- **Decision trade-offs**
  - e.g. incremental harm-benefit ratio (IHBR)

$$IHBR = \frac{\Delta harms}{\Delta benefits} = \frac{harm(strategy_i) - harm(strategy_{i+1})}{benefit(strategy_i) - benfit(strategy_{i+1})}$$

- **Statistical decision theory:** Minimization of loss functions

DECISION MAKING IN POLITICS

- **Political accountability**
  - “good” government → re-election
  - “bad” government → being voted out of office
- **Performance measurement**
  - Data and statistics
- **Political decisions**
  - Understanding of interventions and their causal effects (harms and benefits)
  - Attitudes, perceptions, …
  - Social, ethical, legal aspects

REPORTING AND COMMUNICATION

- **Principles and values** such as accuracy, relevance, timeliness, clarity, coherence, and reproducibility
- For instance **reporting guidelines** in health research: EQUATOR Network (https://www.equator-network.org/)
- **Visual representations**
  - central role in public communication
  - aim to represent content in a quickly understandable manner

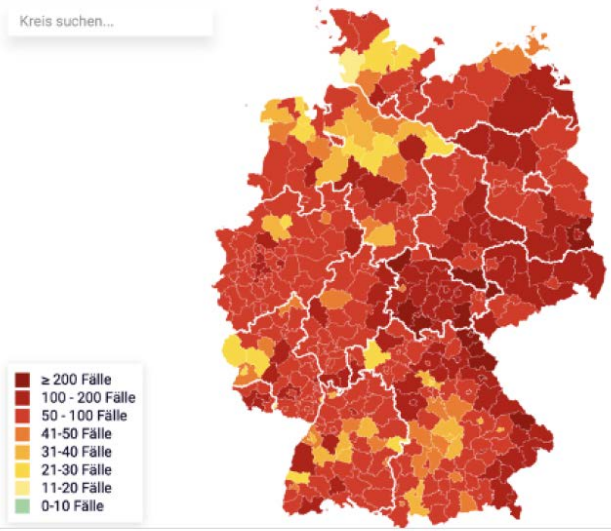

Fig. 3 Choropleth map of the incidence figures for Germany by district. Source: Robert-Koch-Institute https://app.23degrees.io/export/oCRP768wQ3mCswE7-choro-corona-faelle-pro-100-000/image.

Fig.3 from Jahn et al (2021)

PUBLIC ENGAGEMENT

- Reactions to the DAGStat White Paper

Daten • Coronavirus • Datenschutz

Statistiker: Schlechte Daten führen in der Corona-Krise zu schlechten Argumenten

- In der Corona-Krise hängen zahlreiche Entscheidungen von Daten ab – etwa zur Neuinfektionen oder Übersterblichkeit.
- Doch ein Problem ist, dass diese oft nicht vergleichbar sind.
- Mehrere Fachgesellschaften fordern deshalb eine nationale Strategie zur Erhebung von Daten – und eine Überprüfung des Datenschutzes.

26.03.2021, 8:14 Uhr

Coronavirus • Daten • Pandemie

„Stehen uns selbst im Weg“: Experte beklagt schlechte Corona-Datenlage in Deutschland

- Fast anderthalb Jahre nach dem Beginn der Corona-Pandemie beklagen Wissenschaftlerinnen und Wissenschaftler noch immer die schlechte Datenlage in Deutschland.
- Die Gründe für die fehlende Arbeit an einer zielgerichteten und systematischen Datenerhebung sind vielen völlig unklar.
- Dabei zeigt etwa Großbritannien, dass die Erhebung großer Datenmengen bei Covid-19-Patienten möglich ist und bei der Pandemiebekämpfung Früchte trägt.

01.07.2021, 8:09 Uhr

SOME THOUGHTS ON CLINICAL RESEARCH

- Vaccines
- Diagnostics
- Prognostic models
- Interventions / Therapies
  - Acute COVID-19
  - LongCOVID

CLINICAL TRIALS IN A PANDEMIC

- Consequences for the trial design

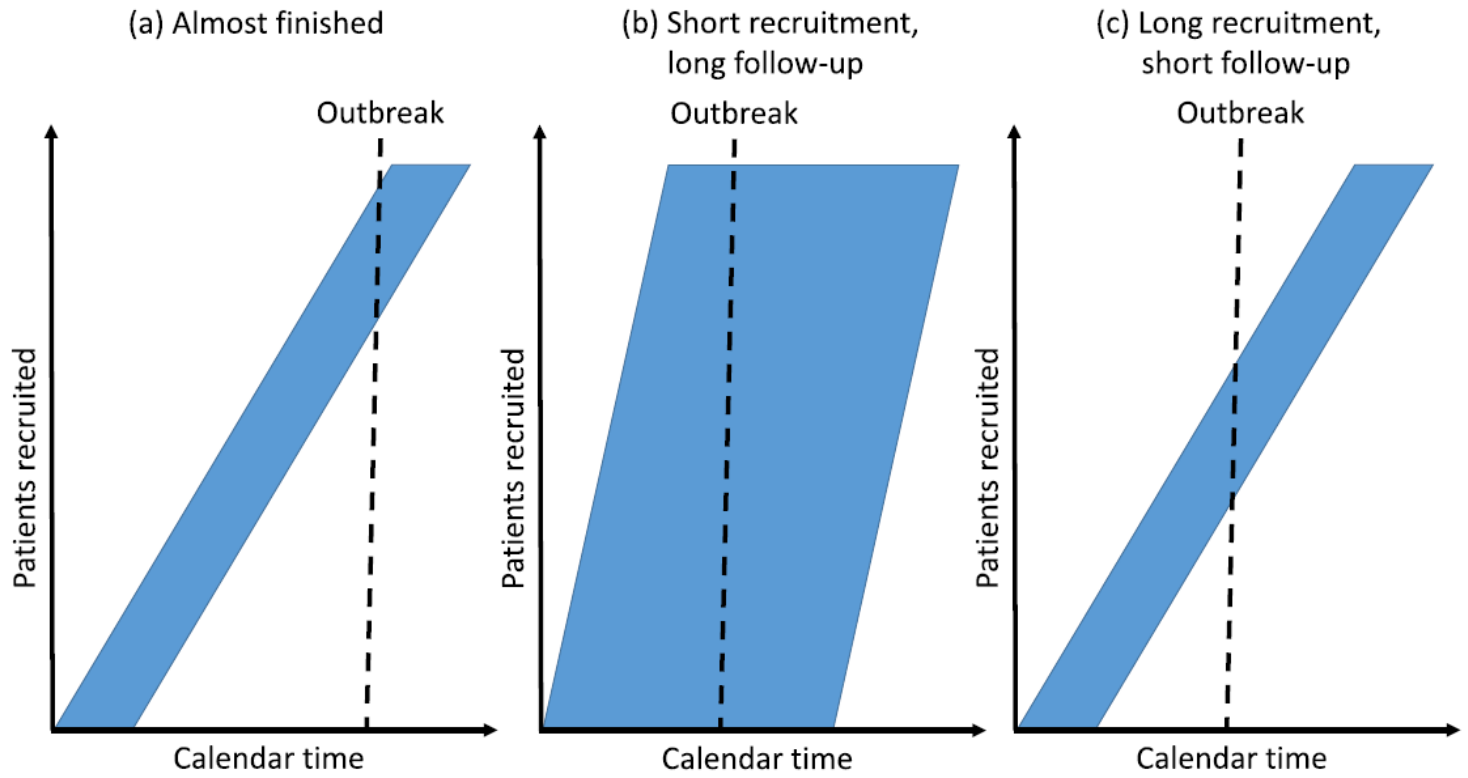

Figure 1. Illustration of how the COVID-19 pandemic impacts clinical trials depending on accrual and follow-up.

Figure 1 from Kunz et al (2020) SBR

CLINICAL TRIALS IN A PANDEMIC

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

- Consequences for data availability / quality
- Heart failure trials during SARS-CoV-2 pandemic

Table 1 **Measurement of endpoints using home-based testing (the current approach for all these measurements is for the patient to attend the research centre and the research team to collect the data)**

Measurement/endpoint category	Example	Alternative method	Validity (high/medium/low/unknown)	Reference
Symptom status	NYHA class	Phone script; smartphone (app-based) self-assessment	Uncertain (patients and HCP score differently)	N/A
Quality of life	KCCQ, EQ-5D	Phone script; emailed link	High for EQ5D	N/A
Adherence	Pill count	Video link with patient	High/medium	N/A
Vital signs	Blood pressure	Home-based cuff	High	George *et al.*[19]
	Heart rate	Patient count; smartphones count; BP cuff count	High	De Ridder *et al.*[17]
	Weight	Home-based scale	High	N/A
	Temperature	Home thermometer	High	N/A
	Oxygen saturation	Home pulse ox by plethysmography on smartphone	High	N/A
ECG	Heart rate and rhythm; QRS	Apple watch; Kardia (Alivecor)	Medium/high; depending on technology and information required	Perez *et al.*[18]
Exercise capacity	6-min walk test	Home-based via app	Medium	Brooks *et al.*[16]
Clinical outcomes	Hospitalization	Retrieve from EMR or central data repository	High	N/A

KCCQ, Kansas City Cardiomyopathy Questionnaire; ECG, electrocardiogram; BP, blood pressure; EMR, electronic medical record; HCP, healthcare providers.

Anker et al (2020) EHJ doi:10.1093/eurheartj/ehaa461

OPPORTUNITIES FOR NOVEL DESIGNS

- **Platform trials**
  - Such as RECOVERY (https://www.recoverytrial.net/)
- **Adaptive designs**
  - Stallard et al (2020) SBR
- **Cross-design evidence synthesis**
  - E.g. combining RCT with observational data (registry, electronic health records, RWE)

DATA MONITORING COMMITTEES

- **Organizational aspects**
  - very frequent meetings: Fast recruitment, new disease / no prior experience / vulnerable population
  - Programme level committees
- **Statistical aspects**
  - Scope and presentation of data
  - Interactive exploration (apps)
  - Monitoring guideline
- **Ref.**: Mütze & Friede (2020) CCT

NYT 14 OCT 20

3 Trials Have Been Paused. That's a Good Thing.

By CARL ZIMMER

This week, two high-profile, late-stage clinical trials — Johnson & Johnson's test of a coronavirus vaccine and Eli Lilly's study of a Covid-19 drug — were put on pause because of possible safety concerns. Just a month earlier, AstraZeneca's vaccine trial was paused after two volunteers became seriously ill.

Clinical trials experts said these delays were comforting, in a way: They show that the researchers were following proper safety procedures. But for now, details about the nature of the volunteers' illnesses are scant. And although pauses of vaccine trials are not unusual, some experts said that pausing treatment trials — like that of Eli Lilly's antibody drug — is rarer, and perhaps more worrisome.

That trial was testing the treatment on hospitalized patients — a group that was already sick, and in which declines in health would not be surprising. So for a trial like that one to be paused, the safety concerns must have been significant, they said.

"I've done 50-plus monitoring committees, and it's quite a rare thing to do," said Tim Friede, a biostatistician at University Medical Center Göttingen in Germany, referring to his role as a safety monitor for drug trials.

For now, the companies behind the trials aren't saying much. In a statement in September, AstraZeneca said it paused its trial to investigate "a single event of an unexplained illness." But two vaccinated volunteers reportedly developed the same condition, an inflammation of the spinal cord called transverse myelitis.

Johnson & Johnson said that it was pausing its vaccine trial because of an "unexplained illness." Eli Lilly's trial of the antibody treatment was paused because of a — so far undisclosed — health difference between the group that received the drug and the group that received a placebo.

When people volunteer for a late-stage trial, known as Phase 3, they randomly get a treatment or a placebo, and neither they nor their doctor knows which one they received. In the weeks that follow, they're carefully monitored. People in a vaccine trial may get a checkup each month and record any symptoms they experience in a journal. People who get a drug while they're hospitalized may be given blood tests and medical exams.

Mild symptoms, like a minor rash or a headache, aren't enough to pause a trial. But when investigators notice a serious problem — known as an "adverse event" — they have to report it to the sponsoring companies. And the sponsors then have to report to both the Food and Drug Administration and their independent advisers, known as data and safety monitoring boards.

If the board or the company judges the adverse event to be particularly concerning, they may put the trial on pause — even without yet knowing if the event happened to someone who got the treatment or the placebo.

Dr. Paul Offit, a professor at the University of Pennsylvania and a member of the F.D.A.'s vaccine advisory panel, said that pausing a trial is a huge logistical challenge — especially for one like Johnson & Johnson's, with plans for 60,000 volunteers in 10 countries.

"It's this big warship that you just stop moving," Dr. Offit said.

Once a trial is paused, a safety board may ask for a volunteer who experienced an adverse event to be "unblinded" — in other words, to find out if the volunteer got the placebo or the treatment. If the volunteer received a placebo, then the treatment can't be the cause of the event and the trial can continue.

If it turns out that the volunteer got the treatment, the board does a flurry of detective work. The members look over the medical records. They may ask for more information about volunteers' health or even order new tests — not just for the people who experienced adverse events, but for everyone in the trial.

The board uses this evidence to come to a conclusion about whether the treatment most likely had anything to do with the event. On very rare occasions, for example, some vaccines can cause a nerve disorder called Guillain-Barré syndrome. But the condition takes weeks to develop. If a volunteer shows signs of Guillain-Barré syndrome on the day of a vaccine injection, it can't be the cause.

Regulators then review the decision of these boards and may accept it or ask for more information. For trials that are running in several countries at once, this review can make pausing a trial even more of a challenge. After AstraZeneca paused its global trials on Sept. 6 for a review, regulators in Brazil, India, Japan, South Africa and the United Kingdom all gave the green light for the trial to resume. But American regulators are still keeping the U.S. trial on pause as they continue to look over the evidence.

If a safety board rules that an adverse event most likely was not a result of the vaccine or treatment, it may allow the trial to start up again. If, on the other hand, there's some urgent problem — a contaminated batch of drugs, for example — the trial may have to stop. When the evidence isn't so clear, the board may let the trial resume with extra tests or exams. A second case of the same event might be more common than you would expect from chance, forcing the trial to end.

But there are some important

ADRIANA ZEHBRAUSKAS FOR THE NEW YORK TIMES

Dr. Yessica Sachdeva working on an antibody drug trial for Eli Lilly in August in Mesa, Ariz. The trial was paused this week.

Experts see signs that safety protocols are being followed.

differences in the way pauses work in trials for vaccines — like Johnson & Johnson and AstraZeneca's — and for drugs like Eli Lilly's. Vaccines are designed to be given to millions or billions of healthy people. So they require extreme safety. If even one person in a vaccine trial gets sick, that warrants a closer look.

"It is not at all uncommon for this to happen," said Dr. Anna Durbin, a professor of international health at the Johns Hopkins Bloomberg School of Public Health. "In the vast majority of cases, the trial continues."

And in a trial as big as Johnson & Johnson's, you expect some sort of adverse event to happen, regardless of the potential risks of the treatment being tested. It would be strange if investigators reported nothing. "Then you're concerned that the surveillance system for adverse events isn't working," said Saad Omer, the director of the Yale Institute for Global Health.

Dr. Stanley Plotkin, a vaccine expert and professor emeritus at the University of Pennsylvania, was not surprised that two vaccine trials were paused. After all, a huge number of vaccine candidates — 43 to date — are being tested in clinical trials. Many of them are based on cutting-edge designs that have never been licensed before. "It means a lot of new ground is being broken," he said, "so people are being doubly careful."

But pauses of treatment trials are not as common. There's a simple reason for the difference: The people getting drugs have a disease, sometimes a very serious one. For Eli Lilly's trial, for example, researchers are only recruiting people who are already hospitalized with Covid-19. In such a group of seriously ill people, even a death would, sadly, not come as a great shock.

As a result, the evidence for an adverse event often has to reach a higher bar to pause a drug trial. Indeed, that seems to be the case with the paused Covid-19 trials. One patient was enough to cause Johnson & Johnson to halt its trial. But a National Institutes of Health spokeswoman said the Eli Lilly trial was paused because the safety board found that the patients who had received the antibodies showed a different "clinical status" than those who had received a placebo.

Dr. Eric Topol, a professor of molecular medicine at Scripps Research in La Jolla, Calif., is still hopeful about the antibody treatment. He observed that Eli Lilly and another company, Regeneron, have already given monoclonal antibodies to thousands of people with Covid-19 without any previous reports of problems (although some of the trials were on people with relatively mild cases). "I'm still fairly optimistic," he said.

Although pausing trials is a standard procedure, it's not a familiar one. Before the pandemic focused the world's attention on clinical trials, researchers would pause trials and investigate adverse events without much notice.

But in a pandemic — especially one in which the president of the United States claims without justification that a vaccine will be ready by Election Day and that monoclonal antibodies are a miraculous "cure" for Covid-19 — these pauses are drawing attention like never before. "That is something we are not used to at all," Dr. Friede said.

Nevertheless, Dr. Friede said, it is vital that researchers stick to their protocols, no matter the pressure they feel to speed things up. "That's a very difficult situation to be in, but I think it's very important that we keep up the standards," he said.

No matter what the outcome of the pauses, many experts found the caution heartening. "It shows me that people are taking safety very seriously," Dr. Durbin said. "This is an example of how things are supposed to work."

RESEARCH STANDARDS

- Keep up research standards!

Deutsche Forschungsgemeinschaft

Statement

DFG 2020
FÜR DAS WISSEN ENTSCHEIDEN

DFG beto
Qualitäts

Vor dem Hint
nen auf Prep
zogen wurde

EDITORIAL

Randomized Clinical Trials and COVID-19
Managing Expectations

Howard Bauchner, MD; Phil B. Fontanarosa, MD, MBA

Despite the millions of cases and hundreds of thousands of deaths that have occurred in this devastating coronavirus disease 2019 (COVID-19) pandemic, no peer-reviewed studies of specific therapies proven to be effective in reducing mortality have been published and a vaccine is many months to years away. To date, more than 1000 studies addressing various aspects of COVID-19 are registered on ClinicalTrials.gov, including more than 600 interventional studies and randomized clinical trials (RCTs).[1] During the next few weeks and months, the results of numerous RCTs involving therapies for ventilation. Few of the studies will be sufficiently powered to detect a difference in mortality. Although these are important clinical outcomes, and use of mechanical ventilation is associated with mortality, it will be important to objectively assess and accurately describe the outcomes from ongoing trials and what the results potentially mean in terms of improving overall survival. In addition, for trials with unblinded treatment allocation and unblinded outcome assessment, interpretation of findings, such as symptom resolution, may be problematic.

DISCUSSION

- **DAGStat White Paper**
  - availability of data: national data infrastructure, representative longitudinal study)
  - transparency
  - interdisciplinary collaboration
  - communication
  - statistical / data literacy
- **A pandemic is not the time to forget about important principles / standards, but to reinforce them**

SOME REFERENCES

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

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- Jahn B et al (2021) From data to decisions: Statistics for pandemic preparedness. (in preparation)
- Mütze T, Friede T (2020) Data monitoring committees for clinical trials evaluating treatments of COVID-19. Contemporary Clinical Trials 98: 106154.
- Stallard N et al (2020) Efficient adaptive designs for clinical trials of interventions for COVID-19. Statistics in Biopharmaceutical Research 12: 483–497.

DAGSTAT 2022

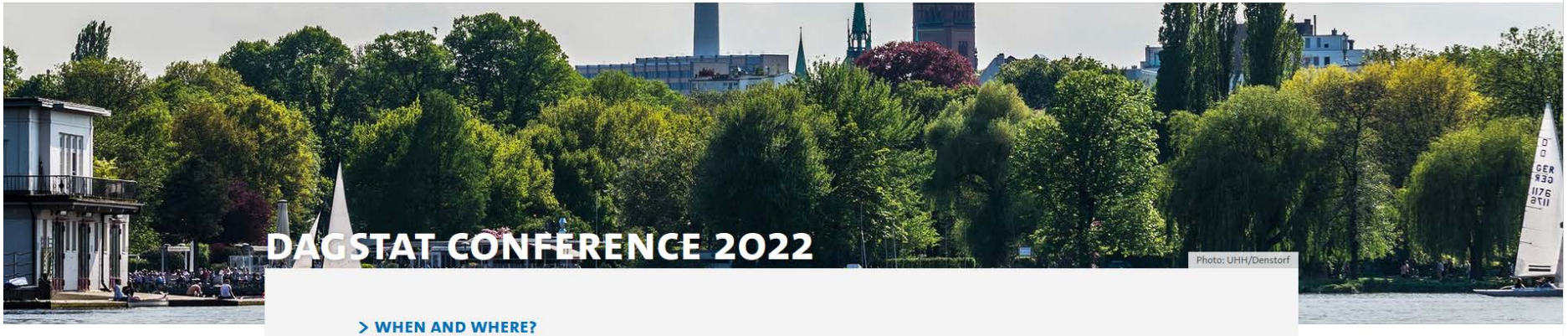
UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

- Hamburg, March 28 – April 2, 2022

DAG STAT

DEUTSCHE ARBEITSGEMEINSCHAFT STATISTIK

CONFERENCE DETAILS | SCIENTIFIC PROGRAM | SOCIAL PROGRAM | TRAVEL & ACCOMODATION | CONTACT



> WHEN AND WHERE?

> KEYNOTE SPEAKERS AND SESSIONS

Welcome

Welcome to the DAGStat Conference 2022! The sixth conference of the Deutsche Arbeitsgemeinschaft Statistik will take place in Hamburg, from March 28 to April 1, 2022. The conference is hosted by the Universität Hamburg in close cooperation with Universitätsklinikum Hamburg-Eppendorf and Helmut-Schmidt-Universität.

The conference is also the 68th Biometric Colloquium of the German Region of the International Biometric Society (IBS-DR) and the 45th annual conference of the Gesellschaft für Klassifikation (GfKl) – Data Science Society.