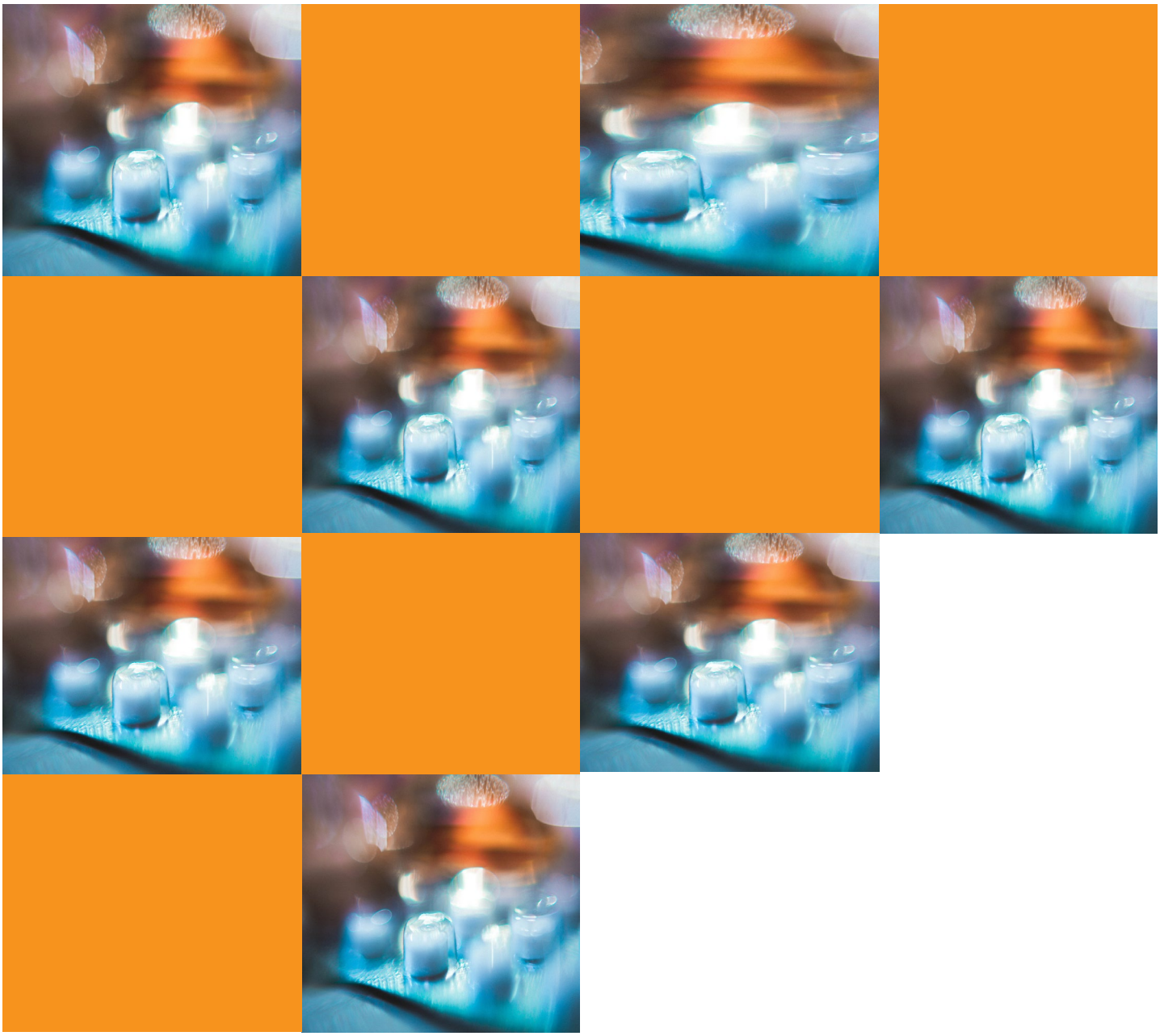

UNIVERSAL ACCESS AND AFFORDABLE MEDICINES

RECOMMENDATIONS:

UNLEASHING INNOVATION THROUGH REGULATORY REFORM

EPHA #A2M DIALOGUES

RECOMMENDATIONS PRODUCED FOLLOWING THE ONLINE DISCUSSION | 19 OCTOBER 2020

epha european public health alliance

About EPHA

EPHA is a change agent – Europe's leading NGO alliance advocating for better health. We are a dynamic member-led organisation, made up of public health civil society, patient groups, health professionals, and disease groups working together to improve health and strengthen the voice of public health in Europe.

About EPHA's Universal Access and Affordable Medicines advocacy

EPHA's Universal Access and Affordable Medicines advocacy promotes transparency, accountability and the public interest in the field of pharmaceuticals in line with the priorities of our members most active in this field. We aim to guarantee better and affordable medicines for Europe by questioning and calling for reforms to the current pharmaceutical business model to ensure better access to medicines for all.

See more at **https://epha.org/universal-access-and-affordable-medicines/**

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Unleashing meaningful innovation through regulatory reform

Recommendations to generate better evidence on new drugs

These recommendations make proposals on how regulatory and payment systems can be adapted to incentivise the timely generation of quality comparative data on the benefits and harms of new drugs and high-risk devices both before and after their market entry, profiting patients, clinicians, and healthcare systems.

They were developed during the the first of the EPHA #A2MDialogues **"Unleashing meaningful innovation through regulatory reform"** by the panelists:

Andrea Cipriani MD PhD, Professor of Psychiatry, University of Oxford

Lydie Meheus PhD, Managing Director, Belgian Anticancer Fund

Huseyin Naci, Assistant Professor of Health Policy, London School of Economics and Political Science

Beate Wieseler, Head, Drug Assessment Department,Institute for Quality and Efficiency in Health Care (IQWiG)

The EPHA #A2MDialogues are a new series of online discussions on key access to medicines (A2M) priorities bringing together thought leaders and policy-makers, academics, industry representatives and NGOs, for a frank discussion of European pharmaceutical policies.

For more information visit: **https://epha.org/epha-a2m-dialogues/**

Unleashing meaningful innovation through regulatory reform

Recommendations to generate better evidence on new drugs

Recommendations for the immediate term

Recommendation 1

Regulators should routinely inform patients and clinicians about what is and is not known about the benefits and harms of new drugs at the time of approval.

- Currently, written drug information sources (for clinicians and patients) in Europe do not disclose uncertainties in drug benefits at the time of marketing authorisation.[1]
- Summary of Product Characteristics, Patient Information Leaflets and European Public Assessment Report summaries for the public should disclose in lay terms all evidence limitations and uncertainties at the time of approval.

Recommendation 2

Regulators should proactively encourage companies to harmonise the designs of clinical trials within each therapeutic area.

- Currently, regulatory scientific advice represents a missed opportunity, as it focuses on a single product's clinical trial portfolio.[2]
- The European Medicines Agency (EMA) should require manufacturers seeking approvals in similar therapeutic indications to adopt similar clinical trial designs, populations, outcomes and follow-up durations.
- If trials share key design features, their utility for health technology assessment bodies and payers would be substantially improved.[3]

Recommendations for the medium term

Recommendation 3

The European Medicines Agency should routinely require individual participant level data on clinical trials supporting its approval decisions, and allow re-analysis of this data by a pre-defined set of third-party organisations.

- Currently, the EMA does not require manufactures to submit individual participant level data from clinical trials supporting its approval decisions.

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1 Dickinson, R., Raynor, D.K., Knapp, P. and MacDonald, J., 2017. How much information about the benefits of medicines is included in patient leaflets in the European Union?–A survey. *International Journal of Pharmacy Practice*, *25*(2), pp.147-158

2 Naci, H., Salcher-Konrad, M., Kesselheim, A.S., Wieseler, B., Rochaix, L., Redberg, R.F., Salanti, G., Jackson, E., Garner, S., Stroup, T.S. and Cipriani, A., 2020. Generating comparative evidence on new drugs and devices before approval. *The Lancet*, *395*(10228), pp.986-997.

3 Naci, H. and O'Connor, A.B., 2013. Assessing comparative effectiveness of new drugs before approval using prospective network meta-analyses. *Journal of clinical epidemiology*, *66*(8), p.812.

- The EMA should become a 'European Data Hub' for clinical trials to maximise learnings from this data beyond the individual trial research question. In addition to supporting development of new drugs, this data could also be used for comparative effectiveness research by a pre-defined range of third parties (e.g., HTA-organisation networks) to inform health care systems.

Recommendation 4

Adaptive platform trials should be used to generate timely comparative evidence on multiple drugs in suitable indications.

- Often more than one drug is developed in parallel in a given indication. Typically, each drug is investigated in isolation, missing a key opportunity to efficiently evaluate multiple drugs simultaneously.
- For indications with small patient populations, EMA, with input from European Health Technology Assessment bodies, should establish platform trials and require that suitable drug candidates are tested in this environment rather than in isolated insufficient trials.
- This approach could increase clinical trial efficiency and ensure early generation of comparative evidence to support decision making also for patients in rare diseases.[4]

Reforming the 'Conditional Marketing Authorisation' pathway

Recommendation 5

Regulators should be more selective in approving drugs on the basis of incomplete benefit and harm data.

- Currently, drugs with incomplete data and uncertain therapeutic benefits often receive regular approval.[5]
- When only incomplete data are available, EMA should routinely use the 'conditional marketing authorisation' pathway.

Recommendation 6

When drugs are conditionally approved on the basis of limited data, post-approval randomised trials should be routinely required to address those limitations.

- Currently, post-marketing studies are not designed to address the limitations of the evidence base at the time of marketing authorisation.[6]
- EMA, with input from European Health Technology Assessment bodies, should require randomised controlled trials that directly address the uncertainties outlined in written drug information sources (see also Recommendation 1).

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4 Angus, D.C., Alexander, B.M., Berry, S., Buxton, M., Lewis, R., Paoloni, M., Webb, S.A., Arnold, S., Barker, A., Berry, D.A. and Bonten, M.J., 2019. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nature Reviews Drug Discovery*, *18*(10), pp.797-808.

5 Salcher-Konrad, M., Naci, H. and Davis, C., 2020. Approval of cancer drugs with uncertain therapeutic value: a comparison of regulatory decisions in Europe and the United States. *The Milbank Quarterly*.

6 Banzi, R., Gerardi, C. and Garattini, S., 2017. Conditional approval of medicines by the EMA. BMJ, j2062.

Recommendation 7

In the post-marketing period, manufacturers should design their studies hierarchically: priority should be given to studies aimed at evaluating a product's net clinical benefit in randomised trials compared with current known effective therapy.

- Currently, manufacturers have no incentive to invest in research to demonstrate the added therapeutic benefit of their products in the post-marketing period. Much of post-marketing research focuses on seeking new indications.[7]
- The EMA, with input from Health Technology Assessment bodies, should encourage companies (even when approval is not conditional) to conduct active-comparator randomised trials.

Recommendation 8

Post-marketing study requirements should be more actively reinforced by regulators.

- Currently, a considerable proportion of required post-marketing studies are not completed in a timely manner.[8]
- Manufacturers should be held accountable for demonstrating and confirming clinical benefits of their products for approved indications.
- Regulators should actively consider license suspensions, indication restrictions, monetary fines, or even market withdrawal.

Recommendations for payers and governments

Recommendation 9

Payers should use their policy levers and negotiating power to incentivise the generation of better evidence on new and existing drugs, for example, by explicitly considering proven added benefit in pricing and payment decisions.

- Currently, there is no clear association between drug prices and demonstrated therapeutic benefit.[9]
- Health Technology Assessment bodies and payers across Europe should routinely disclose information on the comparative benefits and harms of new and existing drugs and whether there is proven added benefit. Experience to date from Germany and France could help other HTA bodies in the future.
- Information on proven added benefit should be a core consideration in pricing negotiations.

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7 Cipriani, A., Ioannidis, J.P., Rothwell, P.M., Glasziou, P., Li, T., Hernandez, A.F., Tomlinson, A., Simes, J. and Naci, H., 2020. Generating comparative evidence on new drugs and devices after approval. The Lancet, 395(10228), pp.998-1010.

8 Banzi, R., Gerardi, C. and Garattini, S., 2015. Approvals of drugs with uncertain benefit–risk profiles in Europe. European journal of internal medicine, 26(8), pp.572-584.

9 Vokinger, K.N., Hwang, T.J., Grischott, T., Reichert, S., Tibau, A., Rosemann, T. and Kesselheim, A.S., 2020. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost–benefit analysis. *The Lancet Oncology*, *21*(5), pp.664-670.

Recommendation 10

Efficiency of randomised trials should be improved by using data from clinical practice and by streamlining patient recruitment and data collection through innovative trial designs (e.g., registry-based randomised trials).

- Currently, complexity and cost of randomised trials is an oft-cited impediment to their implementation in certain therapeutic areas.
- Randomised trials are feasible and have been conducted even in extremely rare conditions. [10]
- Manufacturers should relax trial eligibility criteria to reflect patients in actual clinical practice.
- Data collection should be simplified by leveraging existing registries and other routinely available data sources in health care systems.
- Governments should directly support and facilitate the production of comparative post-marketing data by investing in the development of collaborative research networks and data systems that reduce the complexity and cost of rigorous randomised trials in the post-marketing period.

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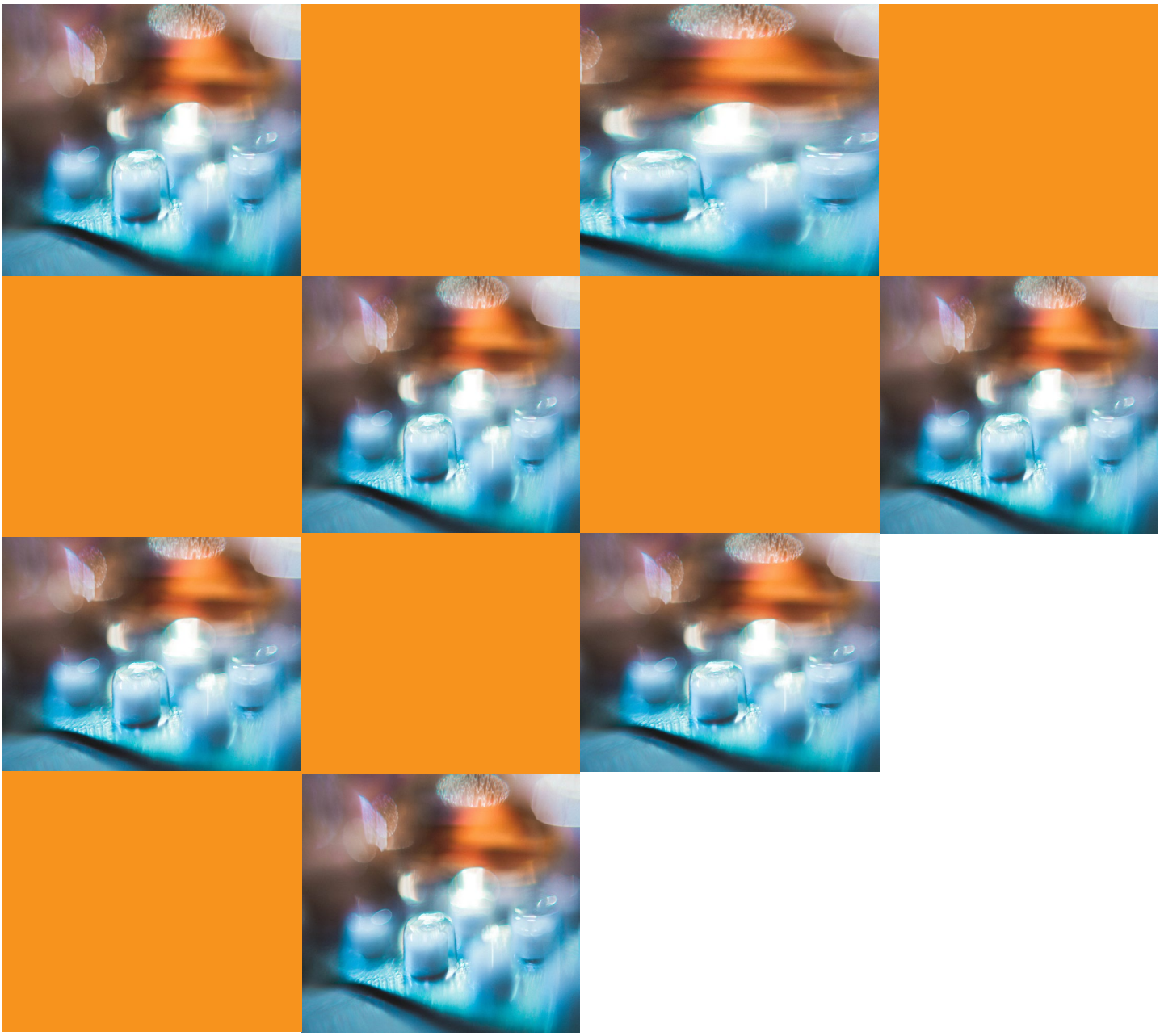
10 Hee, S.W., Willis, A., Smith, C.T., Day, S., Miller, F., Madan, J., Posch, M., Zohar, S. and Stallard, N., 2017. Does the low prevalence affect the sample size of interventional clinical trials of rare diseases? An analysis of data from the aggregate analysis of clinicaltrials.gov. *Orphanet journal of rare diseases*, *12*(1), p.44.



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