

FDA Approval vs. Emergency Use Authorization

- Product Approval – substantial evidence of safety and effectiveness demonstrated by adequate and well-controlled trials, and manufacturing must meet reliability and purity standards.
 - Totality of evidence demonstrates product is safe and effective for intended use
- Emergency Use Authorization – known and potential benefits outweigh the known and potential risks, including manufacturing purity and reliability
 - Totality of evidence demonstrates product may be effective (benefits outweigh risks) to treat serious or life-threatening disease in a public health emergency

FDA Emergency Use Authorizations

b. Evidence of Effectiveness

Medical products that may be considered for an EUA are those that "may be effective" to prevent, diagnose, or treat serious or life-threatening diseases or conditions that can be caused by a CBRN agent(s) identified in the HHS Secretary's declaration of emergency or threat of emergency under section 564(b). Potential EUA products also include those that may be effective to mitigate a disease or condition caused by an FDA-regulated product (including a product authorized for emergency use under section 564 or an approved product) used to diagnose, treat, or prevent a disease or condition caused by a CBRN agent.

¹⁹ The Secretary of HHS publishes in the Federal Register notice of each EUA declaration justifying issuance of an EUA, with an explanation of the basis of the declaration under section 564(b)(1), as well as any advance notice of termination of such a declaration.

²⁰ For general information on expanded access mechanisms, see <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>.

FDA Emergency Use Authorizations

c. Risk-Benefit Analysis

A product may be considered for an EUA if the Commissioner determines that the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product. In making this assessment, FDA must take into consideration the material threat posed by the CBRN agent(s) identified in the HHS Secretary's declaration of emergency or threat of emergency if applicable (section 564(c)).

In determining whether the known and potential benefits of the product outweigh the known and potential risks, FDA intends to look at the totality of the scientific evidence to make an overall risk-benefit determination. Such evidence, which could arise from a variety of sources, may include (but is not limited to): results of domestic and foreign clinical trials, *in vivo* efficacy data from animal models, and *in vitro* data, available for FDA consideration. FDA will also assess the quality and quantity of the available evidence, given the current state of scientific knowledge. The types of evidence that FDA may consider and that should be submitted to support a request for an EUA are discussed more fully in section III.D.2 of this guidance.

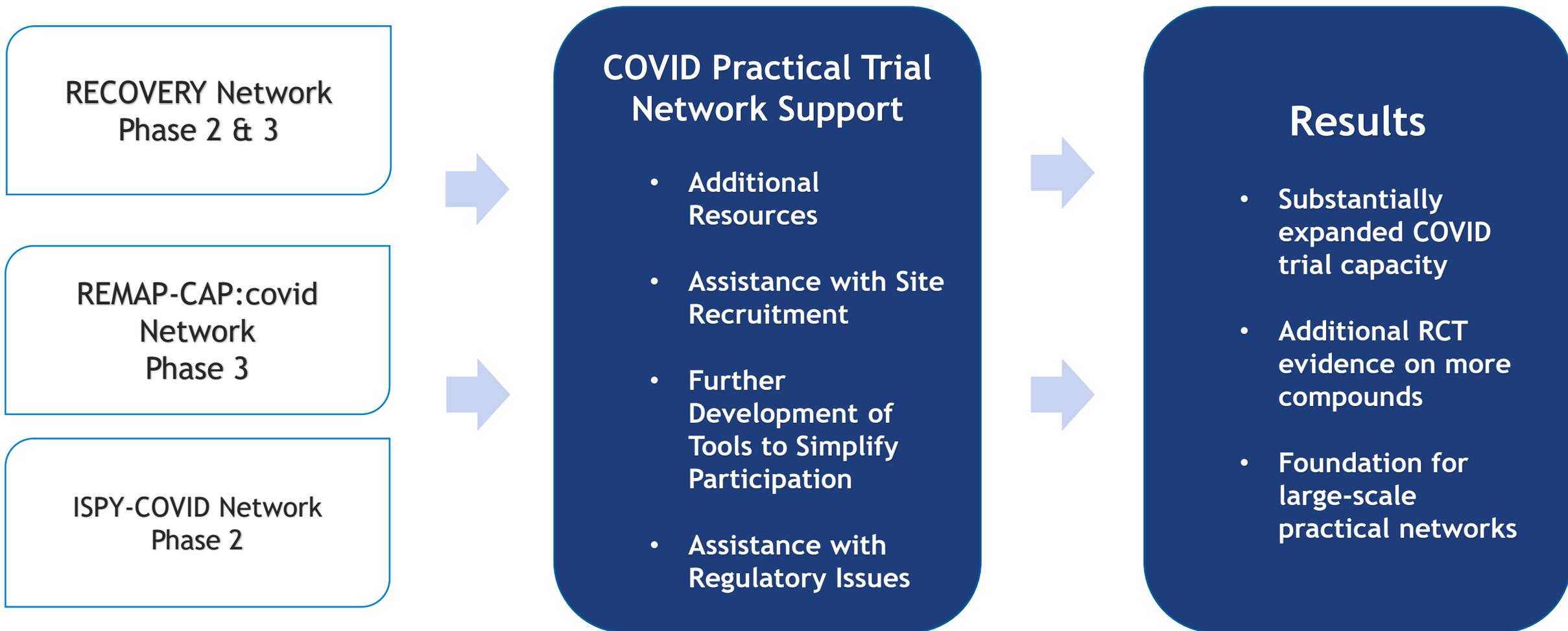
Product Approval vs. Emergency Use Authorization

- Emergency Use Authorization – the known and potential benefits outweigh the known and potential risks, including manufacturing purity and reliability.
 - Emergency use may be authorized for specific populations —such as those at higher risk including healthcare workers—or potentially for a broader population.
- EUA offers FDA flexibility regarding approval standards:
 - For convalescent plasma, FDA authorized emergency use based largely on observational data analysis, and could be augmented/refined through additional observational analysis
 - For COVID-19 vaccines, FDA plans to issue an EUA only once clinical studies have demonstrated the safety and effectiveness of the vaccine.

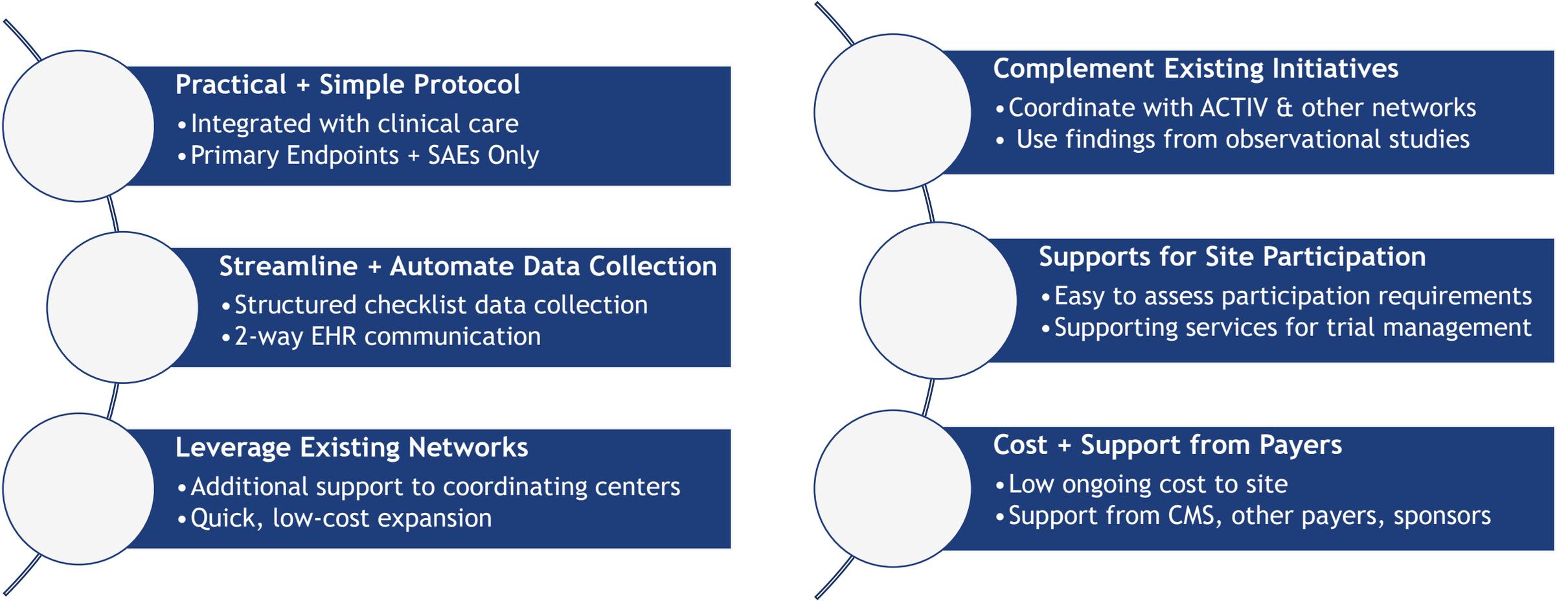
Randomized Clinical Trials in a Pandemic

- Individual Trials
 - Potentially quick to set up
 - Challenges in consistent design, patient enrollment to reach meaningful endpoints and impact
- Trial Networks
 - Extensive effort through ACTIV and Operation Warp Speed to develop and implement scaled, well-designed trials of priority compounds
- Practical Trials
 - Designed
 - For COVID-19 vaccines, FDA plans to issue an EUA only once clinical studies have demonstrated the safety and effectiveness of the vaccine.

Building a Practical Trial Network



Key Features of Practical Trial Protocol



Practical + Simple Protocol

- Integrated with clinical care
- Primary Endpoints + SAEs Only

Streamline + Automate Data Collection

- Structured checklist data collection
- 2-way EHR communication

Leverage Existing Networks

- Additional support to coordinating centers
- Quick, low-cost expansion

Complement Existing Initiatives

- Coordinate with ACTIV & other networks
- Use findings from observational studies

Supports for Site Participation

- Easy to assess participation requirements
- Supporting services for trial management

Cost + Support from Payers

- Low ongoing cost to site
- Support from CMS, other payers, sponsors

Augment Evidence at Product Approval or EUA by Building on Existing Common Data Models and Data Networks

Real World Data Sources / Data Elements

- Secondary electronic data generated through care delivery (e.g., claims and EHR)
 - Single sites
 - Data network
- Primary data sources generated through provider and patient-powered registries

Data Capture Tools / Curation

- Innovative tools to capture and curate data (e.g., NLP)
- CRFs
- Common data element shells
- Common data models

Data Infrastructure

- Data aggregation (e.g., platforms, registries, integrated dataset)
- Data sharing platforms

Analytics

- Data analysis platforms
- Shared protocols and SAPs

Other

- Compiling and Sharing Resources

Enhanced RWE

- Individual Studies
- Parallel Analyses
- Federated / Distributed Research Network
- Virtual Distributed Registries
- Shared Distributed Analysis

Toward a National Strategy for Evidence on Therapeutics in a Public Health Emergency

- **Timely Federal support for well-powered, well-designed trials for clear evidence on priority therapeutics**
 - ACTIV, other global networks aim to reach conclusions where well-designed randomized trials are essential: vaccines, very promising new and existing products
 - Likely to be capacity-constrained
- **Practical trial network that can augment advanced clinical trial network**
 - Phase 2 studies of additional priority compounds, to guide further advanced trial network activity – likely most helpful for non-branded, available products and branded products approved for other indications with established safety profile
 - Phase 3 studies in context where simple trial design can lead to meaningful clinical action (e.g., approved treatments that reduce mortality or other major clinical outcomes in hospitalized patients) or for other important questions beyond capacity of advanced clinical trial networks (e.g., treatment combinations or comparative effectiveness)
 - Leverage co-enrollment capacity for some arms (e.g., REMAP-CAP:covid with ACTIV4)
- **Coordinated efforts to develop evidence from observational real-world studies**