ground states have been proposed theoretically: a valence bond solid (VBS) state with an energy gap in spin excitations (see the figure, panel B) (*6*); a gapped spin liquid (short-range RVB) state (panel C) (*7*); and a gapless spin liquid (long-range RVB) state (panel D) (*8*). A key question is whether the ground state has an energy gap in the spin excitation spectrum.

Fu *et al.* answer this unresolved question by studying a single crystal of a rare mineral, $ZnCu_3(OH)_6Cl_2$ (herbertsmithite), which is an ideal model for the kagome antiferromagnet. Although much experimental work has been carried out since this compound was first synthesized (*9*), the ground state of the compound was not well understood. This is due to the undesirable Cu^{2+} spins (also spin ½) occupying the nonmagnetic Zn^{2+} sites, which prevents the experimental determination of the intrinsic low-energy spin excitation spectrum. Fu *et al.* avoid this problem by using NMR, which can extract the intrinsic magnetic properties. Although NMR has been used to study the compound previously (*10*, *11*), the broad NMR lines typically observed in powder samples hamper precise measurements. Fu *et al.* performed their NMR measurements on a single crystal, yielding much sharper NMR lines than the powder samples could provide. From detailed studies of the single-crystal ^{17}O NMR spectrum, NMR shift, and nuclear spin lattice relaxation time, they were able to conclude that the ground state of the kagome antiferromagnet has a nonzero energy gap, thus excluding model D in the figure.

Fu *et al.* exclude another proposed ground state (the VBS state, model B in the figure) on the basis of the temperature dependence of the x-ray diffraction pattern and the nuclear quadrupole frequency, which is sensitive to lattice distortions. By a process of elimination, they determine that the kagome antiferromagnet possesses a spin liquid ground state with a nonzero spin gap (model C), thus settling the long-outstanding fundamental question and advancing our current understanding of frustrated quantum magnets. ■

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RESEARCH ETHICS

Evidence gaps and ethical review of multicenter studies

Empirical research is needed to guide federal policy

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POLICY

Large, multicenter clinical studies are the backbone of evidence-based prevention and health care. Ethical review of multicenter research is usually conducted by the institutional review board (IRB) of each participating institution. However, variation in interpretation of regulations by IRBs is common and can have ethical and scientific implications (*1*, *2*). Recent mandates in the United States aim to reduce the administrative burden and to expedite multicenter research by conducting ethical review with a single, central IRB of record (CIRB). Yet the quality of ethical review must not suffer. We characterize current models of ethical review in the United States and identify research gaps that must be addressed before such policies are instituted.

Multicenter studies are designed to expedite participant enrollment but are hampered by the current review process. Requests from disparate IRBs to modify study procedures and consent forms may prevent participation of affected centers or require resubmissions to IRBs of all participating centers. Exclusion of clinical centers or modifications to procedures may unequally distribute the benefits and burdens of research.

In September 2015, 16 federal agencies and departments issued a Notice of Proposed Rulemaking (NPRM) that would amend federal regulations to mandate a CIRB for federally funded multicenter research (*3*). The NPRM public comment period ends 7 December 2015. In 2014, the U.S. National Institutes of Health (NIH) issued a draft policy mandating ethical review by a CIRB for NIH-funded multicenter research (*4*). In July 2015, the U.S. House of Representatives passed the 21st Century Cures Act mandating a change in regulations to facilitate CIRBs (*5*).

ALTERNATIVES TO MULTIPLE IRBS. Federal provisions to streamline ethical review of multicenter studies, including use of CIRBs, have been available for years (*6*, *7*). Various streamlined approaches exist in the United States among industry-funded studies, institutions that frequently collaborate, and within universities that have multiple intrainstitutional IRBs (*8*–*10*). Yet, despite evidence that multiple IRB reviews are burdensome and guidance permitting streamlined approaches, CIRBs are rarely used (*10*).

There are several barriers to widespread adoption of CIRBs. Current regulations state that, "In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy." (*7*). Investigators and institutions fear that lack of local IRB review exposes all parties to assertions of noncompliance with federal regulations should there be deficiencies in CIRB review or adverse events (*11*). Under the NPRM, local IRBs are not precluded from conducting ethical review. If local IRBs choose to review despite CIRB review, local IRB review becomes an additional layer, which would extend an already time-intensive process. Guidance on liability for noncompliance when a CIRB is involved must be addressed by an amendment to regulations (*3*, *11*).

> ***"Addressing research gaps is critical to successful implementation of CIRBs for multicenter research."***

Unfamiliarity with local context, as well as delineation of responsibilities of local and central IRBs, are barriers to adoption of CIRBs. (*12*) These barriers are touted by institutional stakeholders, including general counsel, research administration officials, and IRB directors to support the perception that more-streamlined approaches may not provide sufficient protection to participants (*2*).

LESSONS LEARNED. Data on responsibilities, procedures, and performance metrics adopted by existing CIRBs are essential for assessing what aspects of CIRBs are amenable to relevant stakeholders and what

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elements may inhibit implementation. Yet empirical data on principles and practices of CIRBs and other efforts to streamline IRB review in the multicenter setting are scarce (*10*). The NIH is currently supporting research that focuses on the formation and support of, and procedures for, CIRBs (*13*).

The infrastructure of human research protections programs (HRPPs), of which IRBs are one element, should also be studied. HRPPs also oversee investigator training requirements, conflict-of-interest disclosures, and ancillary committees convened when drugs and devices require safety clearance. The challenges of amending procedures and requirements of HRPPs to accommodate CIRB review must not be ignored. Whether administrative burden is relieved by centralized ethical review or merely redirected to negotiating and monitoring multiple CIRB agreements is unknown. Assessments are needed of practice across CIRBs and HRPPs and of factors that predict time to approval of multicenter research.

RESEARCH GAPS. Addressing research gaps is critical to successful implementation of CIRBs for multicenter research.

(i) Nomenclature used to describe models of CIRB review is not uniform and requires clarification (*10*). The term "central IRB review" is used for disparate models and may include independent, federal, and academic IRBs. Other descriptors such as "facilitated," "federated," and "reliant" IRB review are also common.

(ii) Depending on the level of risk of the study, the inclusion of specific populations (e.g., children), or the sensitivity of information to be collected, more-tailored review models may be needed. Procedural heterogeneity is inevitable, but guidance that addresses the complexity of clinical research and is informed by procedures and performance metrics from existing CIRBs is paramount.

(iii) There is no robust measure of quality of IRB review (*15*). The funding agency is responsible for selecting the CIRB under the NPRM. The institution or study chair selects the CIRB when no funding agency exists. Which IRB is selected and whether it will ultimately default to the IRB of the data coordinating center or the IRB of the study chair is unclear. What evidence will inform this decision?

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European Union countries, including the United Kingdom, have used CIRBs for multicenter research as early as 1997 (*14*). Multicenter studies in the United Kingdom are approved, on average, within 35 days, compared with an average response time of 60 days from one IRB before the use of CIRBs (*10*, *14*). Yet the system is flexible enough to allow additional local, site-specific review. Feedback shortly after implementation of CIRBs in the United Kingdom prompted more-detailed guidance on responsibilities of local IRBs (*14*).

A CIRB mandate may promote accreditation, as is done with HRPPs, but there is no empirical evidence that this equates to "higher-quality" review and oversight. Seeking accreditation is time intensive and expensive. The human and financial cost may be prohibitive for smaller HRPPs. Quality domains and metrics from health care–related fields should be explored as starting points for HRPP measures.

(iv) In some instances a CIRB arrangement may be counterproductive because of the need for lengthy negotiations among the participating institutions regarding roles and responsibilities. There are limited data on the structure, content, and time to completion of such negotiated agreements. In a multicenter clinical trial with nine centers, for example, the institutional IRB reliance approval process required 2.5 years for eight centers and 4 years for the ninth center (*8*). Although the time needed to establish such agreements may decrease with time and experience, doing so is unlikely to reduce the administrative burden, as single institutions engaging in multiple reliance agreements will need to devote human and financial resources to coordination and monitoring of such agreements.

The Federal Government has made important first steps by issuing draft policies. In order to make informed decisions before mandates take effect, critical research gaps must be addressed. Recommendations need to be developed on the basis of the findings, and stakeholders, including investigators, must be involved. ■

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