Background Immune-related Adverse Events (irAEs) are rare but serious sequelae of treatment with immuno-oncology (IO) therapeutics. These therapeutics, including monoclonal antibodies targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have had transformative effects on outcomes for patients with advanced cancers. Although most patients tolerate the therapies well, a few experience irAEs ranging in severity up to life-threatening or fatal. These irAEs involve diverse organs including the heart, kidney, liver and lung, and gastrointestinal, musculoskeletal, central and peripheral nervous systems. Because of the relatively low incidence and wide variety of irAEs due to various immunotherapies for multiple tumor types, establishment of an efficient centralized repository for acquisition and organized distribution of well-annotated biospecimens is vital for translational studies that improve understanding of the molecular pathogenesis and treatment of these significant toxicities.

Methods This multi-institutional study is open at sites across the National Clinical Trial Network. Patients may be pre-registered prior to starting IO therapy, or registered when they experience one or more irAEs. Any patient who has not previously been treated with CTLA-4, PD-1 or PD-L1 inhibitors is eligible for pre-registration. These patients provide blood and stool samples prior to starting IO therapy and again after 1 month. Regardless of whether they were pre-registered, patients who received ≥ 1 IO therapeutics (e.g., CTLA-4, PD-1 or PD-L1 inhibitor) and experienced 1) ≥ 1 grade 3–5 irAEs, 2) ≥ 1 grade 2 dermatologic or rheumatologic irAEs, 3) rare infection, or 4) tumor hyperprogression may be registered to the study. IrAEs of interest include myocarditis, colitis, hepatitis, nephritis, myositis, pneumonitis, meningitis/encephalitis, dermatitis, endocrinopathies, neuropathy, other rheumatological, hematologic cytopenias, and pancreatitis. Patients may be on an NCTN or non-NCTN IO trial or be receiving standard-of-care therapy. Registration must occur ≤ 96 hours after confirmation of the irAE. Clinical data are collected at registration, after 1 month after, and for up to 1 year. Biospecimens include archival tumor blocks, biopsies of inflammatory tissues used to establish irAE diagnosis, blood for isolation of plasma and peripheral blood mononuclear cells, and stool samples. Imaging data are collected for patients with hyperprogression, pneumonitis, or other radiographically-diagnosed irAEs. Accrual goal is 2000 pre-registered and 360 registered subjects. As of June 30, 2022, 485 sites have been approved to participate and 88 subjects have been registered. Biospecimens and data will be made available to investigators following future submission and approval of proposals.

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Trial Registration ClinicalTrials.gov NCT04242095

Ethics Approval The study is approved by the National Cancer Institute Central Institutional Review Board.