Supplemental Material for:

Studies of Cannabinoid-Based Products in ClinicalTrials.gov: A Scoping Review

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Supplementary materials

Intervention categories

Drugs included plant-based drugs or synthetic versions of cannabinoid-based products currently approved in at least 1 market (dronabinol, nabilone, nabiximols, cannabidiol). Searches were conducted using these keywords: (1) “nabiximols” OR “Sativex” OR “GW100”; (2) “Epidiolex” OR “GWP42004”; (3) “nabilone” OR “Cesamet” OR “nabilona;
(4) “Marinol” OR “Syndros” OR “dronabinol” OR “Namisol.”

Compounds were defined as extracts with defined content of cannabinoids or nonapproved drug products, with defined content specified as mg/mL or something similar. Products without defined content were included in either cannabis or hemp categories as appropriate. Synthetic cannabinoids, other than synthetic versions of phytocannabinoids, were excluded. Studies investigating a high ratio (defined as ≥20:1) of tetrahydrocannabinol (THC) to cannabidiol (CBD) or vice versa were categorized only by the dominant cannabinoid. Studies that investigated the 1:1 ratio of THC to CBD were categorized as THC:CBD, whereas other ratios <20:1 were categorized as THC/CBD. All investigated cannabinoids were recorded as an intervention if one cannabinoid was not dominant. Searches were conducted using these keywords: (1) “cannabidiol” OR “CBD,” (2) “tetrahydrocannabinol” OR “THC,”

(3) “cannabigerol” OR “CBG,” (4) “cannabinol” OR “CBN,” (5) “cannabichromene” OR “CBC,” (6) “cannabidioloic acid” OR “CBDA,” (7) “cannabigerolic acid” OR “CBGA,” (8) “tetrahydrocannabinolic acid” OR “THCA,” (9) “cannabinolic acid” OR “CBNA,” “cannabidivarin” OR “CBDV,” (10) “tetrahydrocannabivarin” OR “THCV,” (11) “cannabigerovarin” OR “CBGV,” (12) “cannabichromevarin” OR “CBCV,” and (13) “cannabicyclol” OR “CBL.”

Cannabis included all whole cannabis plant products regardless of administration mode, including items such as vape cartridges, which are extracted or modified but not controlled for a specific cannabinoid percentage or content. Products that are smoked or vaped were included, even if they claimed defined cannabinoid content. Products included in the hemp category were excluded from the cannabis category unless they also included a separate intervention classified with the cannabis category. Searches were conducted using the keywords “cannabis” OR “marijuana.”

Hemp included products that self-defined as hemp oil, hemp derived, or “broad spectrum” without the defined cannabinoid content required to be included in the compounds category. Searches were conducted using the keywords “hemp oil” OR “broad spectrum.”

Study phase, recruitment status, and status of availability through expanded access programs (EAPs) were defined per the ClinicalTrials.gov database. Registered status was grouped into active, completed, terminated, and unknown categories to cross-align EAPs and determine overall study status. Studies were classified according to Medical Subject Headings (MeSH) disease category [C] (with the addition of “healthy” per ClinicalTrials.gov parlance) and mental disorders [F03], a subcategory under psychiatry and psychology [F] (**Table S1**). MeSH terms “mental disorders” and “chemical-use disorders” are hereinafter referred to as “psychiatric disorders” and “substance use disorders,” respectively.

Categorization of conditions/diseases and sponsors

Use of MeSH terms is encouraged by ClinicalTrials.gov for the identification of conditions and diseases, but not all studies use these terms. Therefore, the AACT database was used to link clinical data to MeSH terms.

Because of challenges with accurate sponsor attribution in ClinicalTrials.gov, sponsor information was categorized via Clinical Drug Experience Knowledgebase (CDEK) organization name standardization as follows: commercial (companies manufacturing products other than drugs; also includes clinical research organizations), pharmaceutical (companies that solely

manufacture drugs or drug products within the drug approval pathway), academic/hospital (universities, colleges, research institutes, hospitals, medical centers), government (government agencies and institutes), and individual (self-funded), foundation (nongovernment nonprofits and foundations that do not themselves regularly engage in research).

Sponsor type was based on the listed lead sponsor, and the "for-profit" label was adjusted to distinguish pharmaceutical companies filing New Drug Applications from commercial producers of medical cannabis or unregulated products. Additional analyses were conducted to determine whether funder (i.e., organization providing primary funding/support for the study) should be different from sponsor (i.e., organization with authority over the study).

ClinicalTrials.gov study phase definitions

In this review, the study phases were defined using ClinicalTrials.gov definitions:

- Not applicable: Trials without phases (e.g., studies of devices or behavioral interventions). Includes studies listed as "NA" in the ClinicalTrials.gov database as well as blanks (observational studies and EAPs).
- Early phase 1: (formerly listed as "phase 0"). Exploratory studies involving very limited human exposure, with no therapeutic or diagnostic intent (e.g., screening studies, microdose studies).
- Phase 1: Includes initial studies to determine the metabolic and pharmacologic actions of drugs in humans, determine the side effects associated with increasing doses, and gain early evidence of effectiveness; may include healthy participants and/or patients.
- Phase 1/2: Trials that are a combination of phases 1 and 2.
- Phase 2: Includes controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in participants with the disease or condition under study and to determine the common short-term side effects and risks.
- Phase 2/3: Trials that are a combination of phases 2 and 3.
- Phase 3: Includes trials conducted after preliminary evidence suggesting that effectiveness of the drug has been obtained; trials are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug.
- Phase 4: Studies of US Food & Drug Administration (FDA)–approved drugs to delineate additional information, including the drug's risks, benefits, and optimal use, not including studies in nonapproved/new indications.

Study status on ClinicalTrials.gov

ClinicalTrials.gov uses the following definitions for the recruitment status of a clinical trial/study. These definitions are largely adapted from 42 CFR Part 11.[1]

- Not yet recruiting: Participants are not yet being recruited.

- Recruiting: Participants are currently being recruited, whether or not any participants have yet been enrolled.
- Enrolling by invitation: Participants are being (or will be) selected from a predetermined population.
- Active, not recruiting: Study is continuing, meaning participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled.
- Completed: The study has concluded normally; participants are no longer receiving an intervention or being examined (that is, last participant's last visit has occurred).
- Suspended: Study halted prematurely but potentially will resume.
- Terminated: Study halted prematurely and will not resume; participants are no longer being examined or receiving intervention.
- Withdrawn: Study halted prematurely prior to enrollment of first participant.

Expanded access status on ClinicalTrials.gov

ClinicalTrials.gov uses the following definitions for the status of availability through EAPs that allow patients with a serious disease or condition to gain access to an investigational product outside of a clinical trial.

- Available: Expanded access is currently available.
- No longer available: Expanded access was available previously but is not currently available and is not expected to be available in the future.
- Temporarily not available: Expanded access was previously available, is not currently available, but is expected to be available in the future.
- Approved for marketing: Expanded access was available previously but is not currently available because the product has been approved, licensed, or cleared by the FDA.

ClinicalTrials.gov study status options and grouping used in this analysis

The following groups were used to cross-align EAPs/studies and determine overall status of studies for this report: Active (included ClinicalTrials.gov statuses of enrolling by invitation, recruiting, available, active not recruiting, and not yet recruiting), Completed (approved for marketing and completed), Terminated (suspended, terminated, no longer available, and withdrawn), and Unknown (unknown).

Study funder

Additional analyses were performed using the collaborators of a study to determine whether the funder should be different from the sponsor. If there was ≥1 collaborator, the following algorithm,

adapted from Califf et al,[1] was used to assign a single collaborator as the most likely source of funding: Commercial/Pharmaceutical > Government > Academic/Hospital > Individual.

The funder of a study was assumed to be the main sponsor for pharmaceutical, commercial, and government sponsor types, and the funding collaborator (if present) was used for academic/hospital sponsor type.

References

1. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. JAMA. 2012;307:1838-1847.

Table S1. MeSH disease categories

- Healthy
- Infections [C01]
- Neoplasms [C04]
- Musculoskeletal diseases [C05]
- Digestive system diseases [C06]
- Stomatognathic diseases [C07]
- Respiratory tract diseases [C08]
- Otorhinolaryngologic diseases [C09]
- Nervous system diseases [C10]
- Eye diseases [C11]
- Urogenital diseases [C12]
- Cardiovascular diseases [C14]
- Hemic and lymphatic diseases [C15]
- Congenital, Hereditary, and Neonatal Diseases and Abnormalities [C16]
- Skin and connective tissue diseases [C17]
- Nutritional and metabolic diseases [C18]
- Endocrine system diseases [C19]
- Immune system diseases [C20]
- Disorders of environmental origin [C21]
- Animal diseases [C22]
- Pathological conditions—signs and symptoms [C23]
- Occupational diseases [C24]
- Chemically induced disorders[a] [C25]
- Wounds and injuries [C26]
- Mental disorders[b] [F03]

[a]Referred to as substance use disorders in the main text.
[b]Referred to as psychiatric disorders in the main text.
MeSH, Medical Subject Headings.

Table S2. Top 20 most common condition MeSH terms according to primary outcome,[a] excluding studies not investigating a condition[b]

MeSH term	n (%)
Pain[c]	147 (27.3)
Substance-related disorders[d]	68 (12.6)
Epilepsy[e]	60 (11.1)
Multiple sclerosis[f]	35 (6.5)
Neoplasms[g]	34 (6.3)
Schizophrenia/other psychotic disorders[h]	24 (4.5)
Anxiety disorders	19 (3.5)
Stress disorders, traumatic	18 (3.3)
Arthritis	17 (3.2)
Autism spectrum disorder	14 (2.6)
HIV infections	14 (2.6)
Alzheimer disease[i]	13 (2.4)
Compulsive disorders[j]	13 (2.4)
Nutrition disorders[k]	12 (2.2)
Mood disorders[l]	11 (2.0)
Sleep initiation and maintenance disorders	10 (1.9)
Nausea	8 (1.5)
COVID-19	8 (1.5)
Parkinson disease	7 (1.3)
Migraine disorders	7 (1.3)

[a]Includes all unique studies (total studies=825); 137 studies excluded as not investigating a top 20 condition/disease.
[b]Excluded conditions that are not a true disease/condition include healthy (n=43), pharmacokinetics (n=64), and intoxication/abuse potential (n=42).
[c]Pain includes: pain; chronic pain; pain, neuropathic; pain, postoperative; back pain; diabetic neuropathies; musculoskeletal pain; acute pain; cancer pain; chest pain; fibromyalgia.
[d]Substance-related disorders include: opioid-related disorders; alcohol use disorder; substance-related disorders; tobacco use disorder; cannabis misuse.
[e]Epilepsy includes: epilepsy; Dravet syndrome; Lennox-Gastaut syndrome; spasms, infantile; tuberous sclerosis; epilepsies, myoclonic.
[f]Multiple sclerosis includes: multiple sclerosis, muscle spasticity.
[g]Neoplasms include: neoplasms; nervous system neoplasms; breast neoplasms; pancreatic neoplasms; lung neoplasms; head and neck neoplasms; prostatic neoplasms; bone neoplasms; melanoma.
[h]Schizophrenia/other psychotic disorders include: schizophrenia spectrum and other psychotic disorders; psychotic disorders.
[i]Alzheimer disease includes: Alzheimer disease; dementia.
[j]Compulsive disorders include: Tourette syndrome; compulsive personality disorder.
[k]Nutrition disorders include: nutrition disorders; overweight; wasting syndrome.
[l]Mood disorders include: bipolar disorder; mood disorders; depressive disorder.
MeSH, Medical Subject Headings.

Figure S1. Number of records per intervention category by funder type

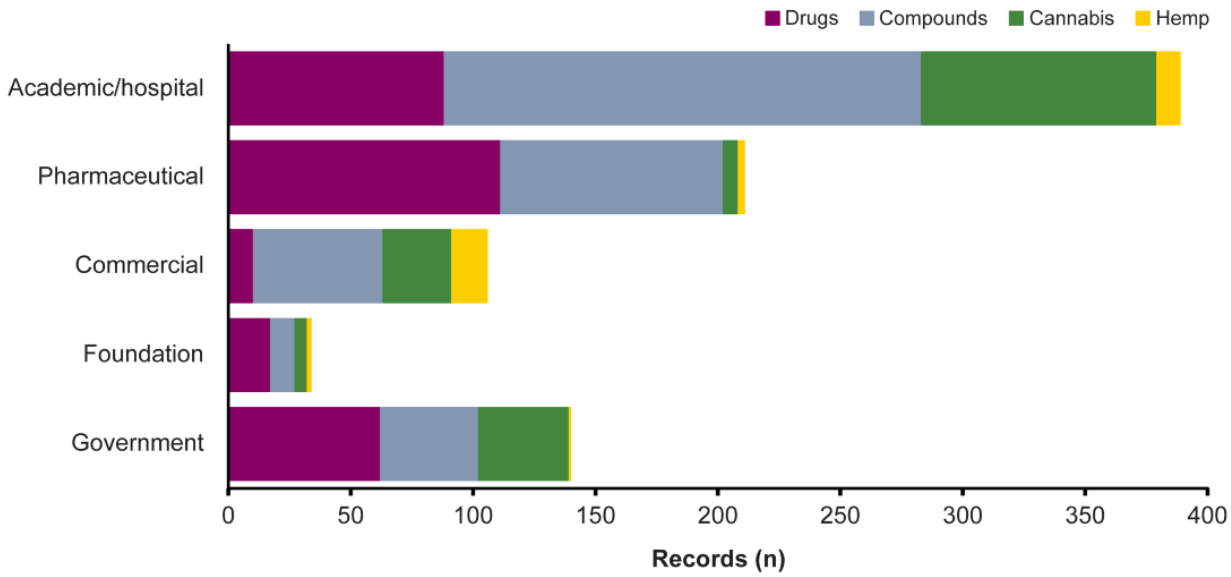
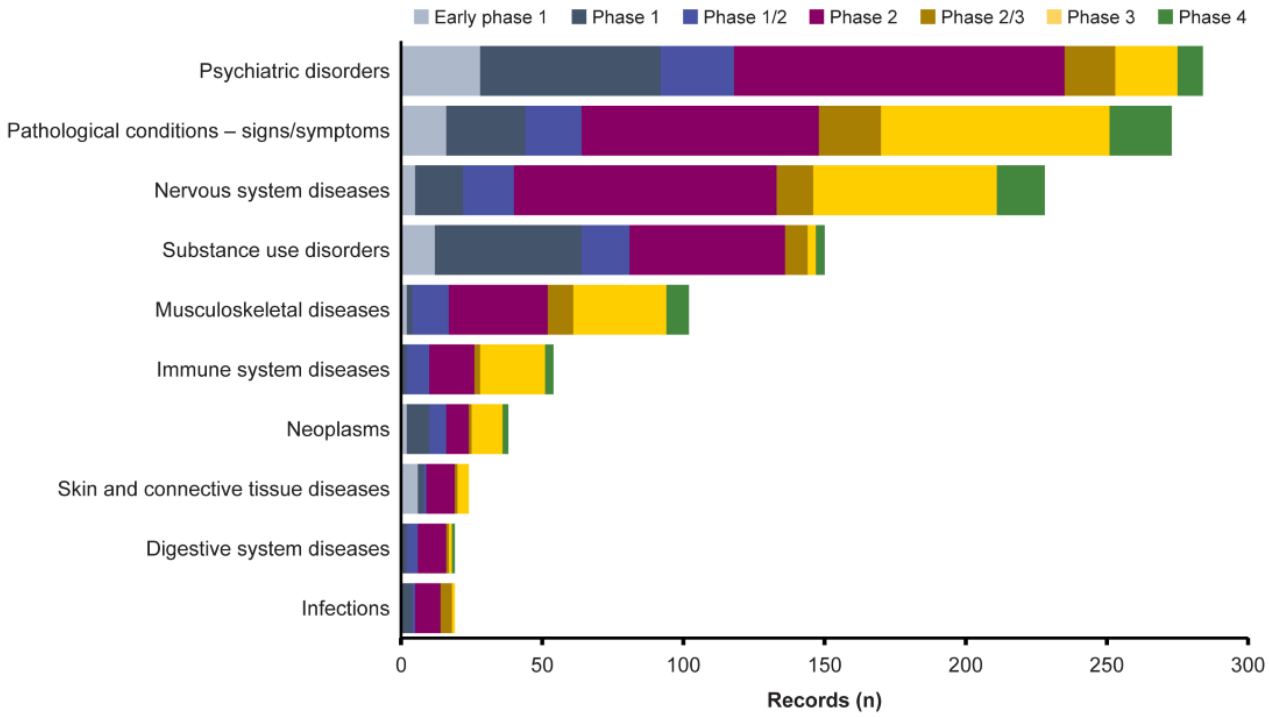


Figure S2. Top 10 most assigned MeSH categories by phase (N=1191)[a,b]



[a]Excluded 163 records with MeSH heading of Healthy and 270 records with Not Applicable as phase; an additional 132 study records with MeSH headings below the top 10 are not shown.
[b]Most studies have >1 assigned MeSH category because of the interconnected nature of MeSH terms.
MeSH, Medical Subject Headings.

Figure S3. Duration of study by (A) intervention category and (B) phase

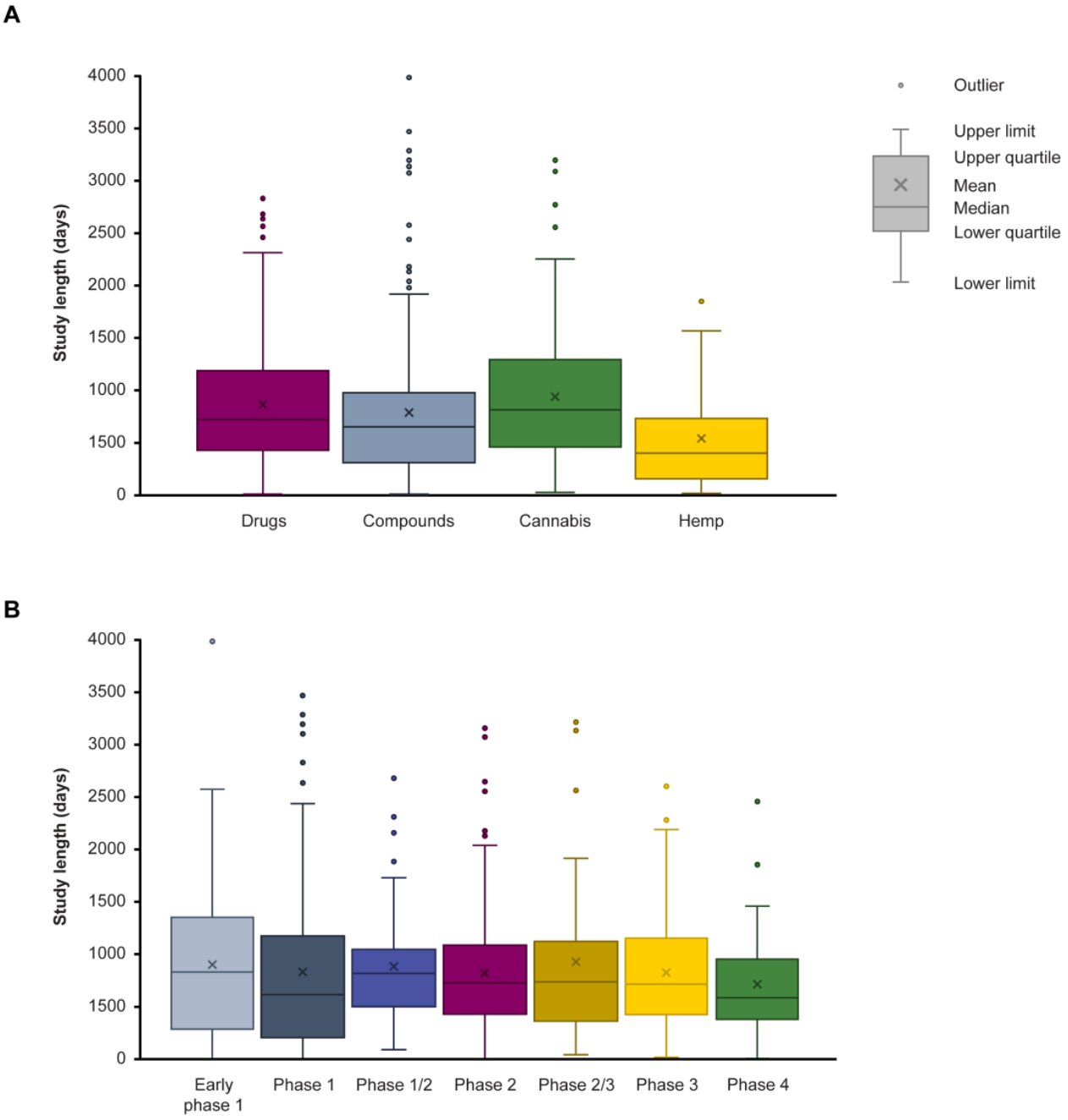


Figure S4. Sponsoring institution by (A) intervention category and (B) phase

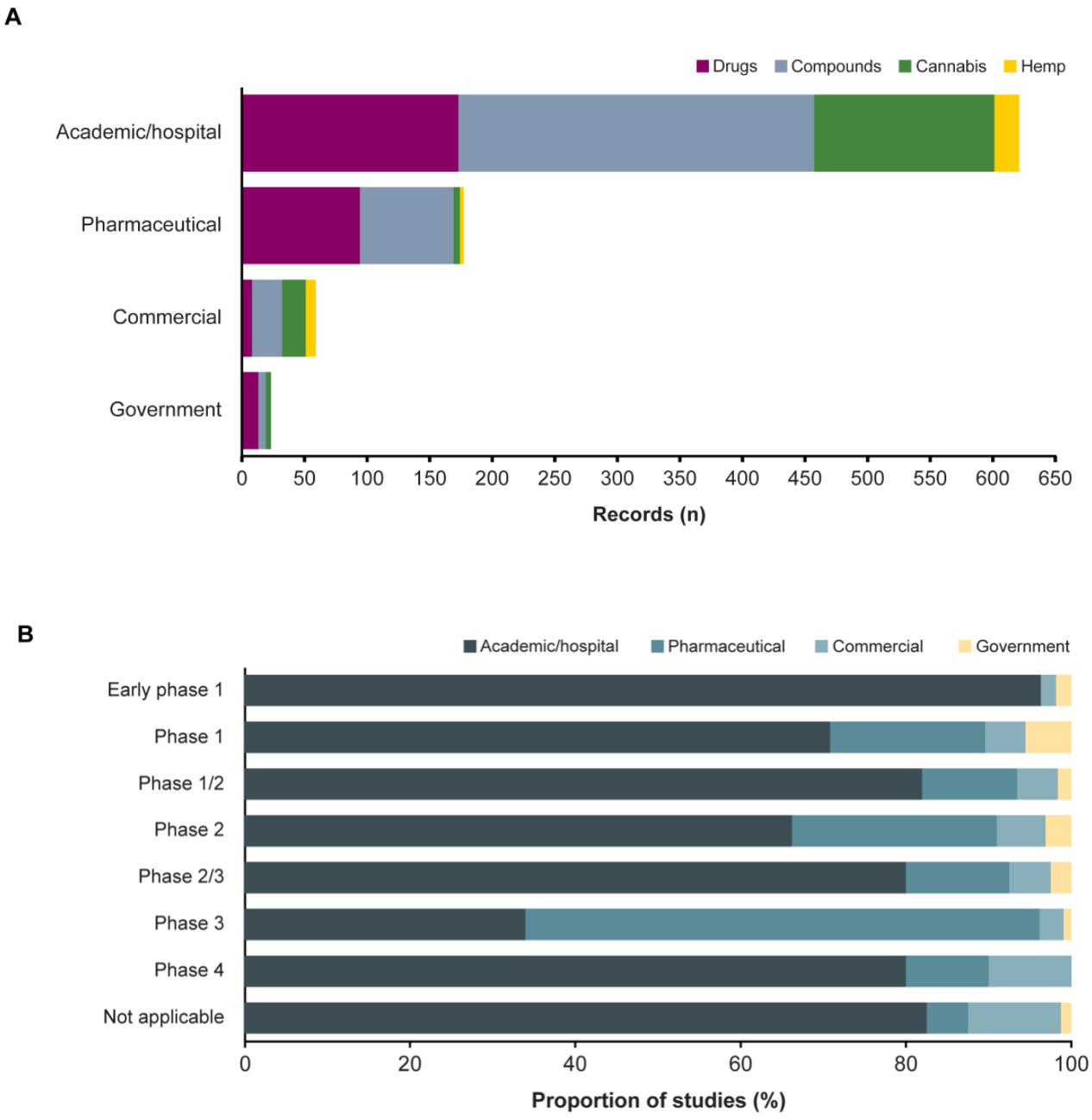
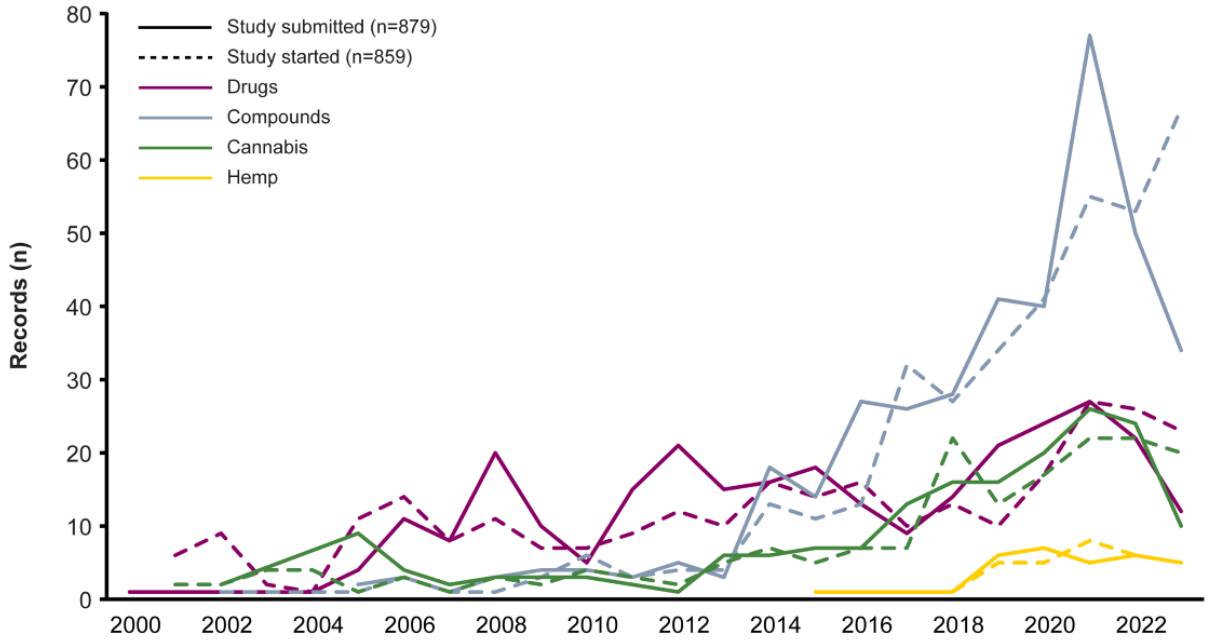


Figure S5. Change in number of study records by category of cannabinoid-based intervention by submission year and study start (actual or estimated)[a,b]



[a]Studies that included multiple interventions are included in the relevant category for each intervention; duplicate records of single studies are included.
[b]Start date analyses excluded 10 studies that did not provide a start date, and 10 studies with a start year after 2023.