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# Use of 55 PET radiotracers under approval of a Radioactive Drug Research Committee (RDRC)

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This article is dedicated to Capt. Richard Fejka, MS, RPh, BCNP, USPHS (Ret.) on the occasion of his retirement after 39 years of government service and 17 years overseeing the RDRC Program at the U.S. Food and Drug Administration.

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## Abstract

**Background:** In the US, EU and elsewhere, basic clinical research studies with positron emission tomography (PET) radiotracers that are generally recognized as safe and effective (GRASE) can often be conducted under institutional approval. For example, in the United States, such research is conducted under the oversight of a Radioactive Drug Research Committee (RDRC) as long as certain requirements are met. Firstly, the research must be for basic science and cannot be *intended* for immediate therapeutic or diagnostic purposes, or to determine the safety and effectiveness of the PET radiotracer. Secondly, the PET radiotracer must be generally recognized as safe and effective. Specifically, the mass dose to be administered must not cause any clinically detectable pharmacological effect in humans, and the radiation dose to be administered must be the smallest dose practical to perform the study and not exceed regulatory dose limits within a 1-year period. In our experience, the main barrier to using a PET radiotracer under RDRC approval is accessing the required information about mass and radioactive dosing.

**Results:** The University of Michigan (UM) has a long history of using PET radiotracers in clinical research studies. Herein we provide dosing information for 55 radiotracers that will enable other PET Centers to use them under the approval of their own RDRC committees.

**Conclusions:** The data provided herein will streamline future RDRC approval, and facilitate further basic science investigation of 55 PET radiotracers that target functionally relevant biomarkers in high impact disease states.

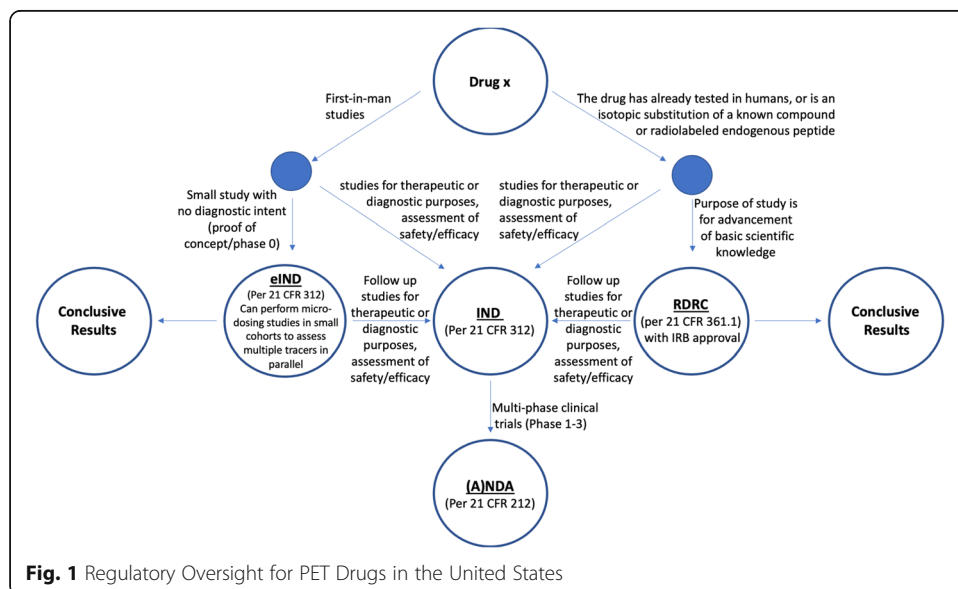
**Keywords:** PET imaging, Regulatory oversight, Dosimetry, RDRC, IND, Radiopharmaceuticals, Quality assurance

## Background

Human use of positron emission tomography (PET) radiotracers in a given country (or member states in the case of the European Union) is required to be conducted under appropriate governmental oversight (Schwarz and Decristoforo 2019; Schwarz et al. 2019). In this paper, we focus upon clinical use of PET radiotracers in the United States, which is regulated by the Food and Drug Administration (FDA) (VanBrocklin 2008; Harapanhalli 2010; Schwarz et al. 2014). However, we expect the regulatory concepts described herein to also hold true in other locations, particularly in light of recent efforts to harmonize PET regulations around the world (Schwarz et al. 2019).

In the US, clinical use of PET radiotracers is conducted under the umbrella of an FDA-approved New Drug Application (NDA) or, in the case of generic PET radiotracers, an Abbreviated New Drug Application (ANDA). Human research is also conducted under governance of the FDA, via three major pathways: i) the Investigational New Drug application (IND), ii) an exploratory IND (eIND), or iii) under the oversight of a Radioactive Drug Research Committee (RDRC) (Suleiman et al. 2006; FDA Guidance for Industry and Researchers: The Radioactive Drug Research Committee: Human Research without an Investigational New Drug Application 2010; Carpenter Jr et al. 2009; Mosessian et al. 2014). The necessary path to approval is dictated by parameters outlined below, as well as the stated purpose of the research in question (Fig. 1).

While the IND and eIND represent the most common pathways to FDA approval for first-in-man studies, some of the requirements (e.g., costly toxicology in two species for an IND) represent significant hurdles to overcome in the application process. One notable solution, as described by Mosessian et al., is to divide labor and preparation for different components of the application between different cores and facilities at a given institution (Mosessian et al. 2014). In contrast, conducting human PET research under RDRC oversight represents a relatively efficient and cost effective path to FDA approval. The concept of the RDRC was introduced in 1975, and committees are charged by the FDA with the responsibility of overseeing PET research at the institutional level.



**Fig. 1** Regulatory Oversight for PET Drugs in the United States

RDRC committees are comprised of at least 5 members and are required to include people with the following expertise:

- Physicians specializing in nuclear medicine;
- Nuclear pharmacists and/or radiochemists that are trained and qualified to formulate radioactive drugs;
- Persons having training in radiation safety and radiation dosimetry;
- Individuals specializing in disciplines pertinent to nuclear medicine (radiology, internal medicine, hematology, endocrinology, radiation therapy, clinical pharmacology, etc.).

In order for a given PET imaging study to be conducted under RDRC approval, the proposed research must meet the following criteria (as described comprehensively in 21 CFR 361.1):

- Stated purpose of the research must fall under the category of basic science, including but not limited to studies of: metabolism, kinetics, biodistribution, pathophysiology, biochemistry, transporter processes, and receptor binding/occupancy.
- The research cannot be *intended* for immediate therapeutic or diagnostic purposes, or to determine the safety and effectiveness of the PET radiotracer, but can have therapeutic/diagnostic *implications*. If at any point research initiated under RDRC approval shifts to directly address these subjects, IND approval must be obtained prior to further studies.
- The protocol must involve less than 30 patients, of age 18 or older (exceptions possible pending special approval), and women of child bearing potential must provide a written statement that they are not pregnant (without exception).
- The PET radiotracer is generally recognized as safe and effective (GRASE).

Specifically:

- The mass dose to be administered must not cause any clinically detectable pharmacological effect in humans. It is important to note that this generally precludes first-in-human testing of a PET radiotracer from being done under RDRC approval. Notably, RDRC approval can be used for study of radiolabeled endogenous molecules, as well as isotopic substitutions on clinically characterized compounds (i.e; substituting  $^{18}\text{F}$  for  $^{19}\text{F}$  on a small molecule ligand that has previously been approved and studied by the FDA, often via IND)
- The radiation dose to be administered must be the smallest dose practical to perform a given study. Specifically, the radiation dose to an adult research subject from a single study, or cumulatively from a number of studies, conducted within 1 year may not exceed established regulatory dose limits:

(a) Whole Body / Active Blood-Forming Organs / Lens of Eye / Gonads: Single Dose (Effective Dose) = 3 rem (0.03 Sv), Annual & Total Effective Dose Commitment = 5 rem (0.05 Sv);

(b) Other Organs: Single Dose = 5 rem (0.05 Sv); Annual and Total Dose Commitment = 15 rem (0.15 Sv).

The radiation dose to a subject consists of the sum total of all sources of radiation associated with the research protocol, including the PET radiotracer(s),

associated x-ray procedures (including CT scans, PET transmission scans etc.) and any follow-up studies.

- For research subject under 18 years of age at his or her last birthday, the RDRC regulations require that the radiation limits do not exceed 10% of the radiation dose values given above.
- Other key criteria as described in 21 CFR 361.1 include providing evidence of: Qualified investigators, high quality of drug, research protocol, appropriate licensure to handle radioactive material, and review/approval for work with human subjects (via the Institutional Review Board (IRB)).

If all of these criteria are met, then the research can proceed following RDRC and IRB approval. Research conducted in RDRC studies is considered basic science. Specifically, basic science research is intended to advance scientific knowledge, but not to evaluate safety or efficacy of a PET radiotracer or to make clinical decisions. Failure to meet this, or any of the other RDRC criteria outlined above, necessitates that the research be conducted under an IND or eIND application that has been approved by the U.S. Food and Drug Administration (FDA), as outlined in 21 CFR 312 (Mosessian et al. 2014).

To ensure compliance with the pertinent regulations, FDA vests RDRC committees with oversight responsibility for basic science research conducted at the committee's institution. The committee reviews and approves research protocols to ensure compliance with RDRC regulations, and submits annual reports to FDA that list committee members and summarize all studies conducted under the committee's approval in the preceding year. The RDRC committee must also submit a special summary (Form FDA 2915) for any approved study involving > 30 research subjects (Suleiman et al. 2006).

Conducting human PET imaging under RDRC approval represents a straightforward and economical pathway to clinical use, particularly since there is no requirement for resource intensive pharmacology-toxicology studies. In our experience, the main barrier to using a PET radiotracer for basic science under RDRC approval is actually accessing the required information about pharmacological dose/mass and radioactive dose. For a given radiotracer this information can either come from the peer-reviewed scientific literature or other valid data, often in the form of a signed letter from an institution already working with the radiotracer in question. In an effort to remove barriers to those wishing to conduct clinical PET research under RDRC, herein we provide pharmacological dose and radioactive dosimetry details for 55 such PET radiotracers that will enable other PET Centers to use them under the approval of their own RDRC committees, eliminating the need to obtain a specific signed letter on a case-by-case basis. The article is made available Open Access in an attempt to further improve accessibility for our imaging colleagues, and we encourage other PET Centers with large clinical radiotracer portfolios to publish sister articles in the near future.

## Methods

### Radiosyntheses

PET radiotracers were commercially available, or synthesized according to the literature radiosyntheses referenced in Table 1 or novel radiosyntheses described in the [Supporting Information](#). Production and quality control of all radiotracers was conducted

**Table 1** Radiotracers used clinically at the University of Michigan

Radiotracer	Abbreviation	Application	Radiosynthesis	Dosimetry	Historical Imaging
<b>[<sup>11</sup>C]Radiotracers</b>					
[ <sup>11</sup> C]Acetate	[ <sup>11</sup> C]ACE	Metabolism	Runkle et al. 2011	Seltzer et al. 2004	Duvernoy et al. 2016
[ <sup>11</sup> C]Aminocyclohexane carboxylic acid	[ <sup>11</sup> C]ACHC	Amino acid transport	Koeppel et al. 1990a	Washburn et al. 1982 <sup>a</sup>	Koeppel et al. 1990a
1-[ <sup>11</sup> C]Methyl-4- piperidyl n-butylate	[ <sup>11</sup> C]BMP	Butyrylcholinesterase	Snyder et al. 2001	Virra et al. 2008	Kuhl et al. 2006
[ <sup>11</sup> C]Butanol	[ <sup>11</sup> C]BUT	Blood flow	See Supporting Information	See Supporting Information	<sup>b</sup> ; Quatles et al. 1993
[ <sup>11</sup> C]Carfentanil	[ <sup>11</sup> C]CFN	Mu opioid receptors	Blecha et al. 2017	Newberg et al. 2009	Zubieta et al. 2000
[ <sup>11</sup> C]Choline	[ <sup>11</sup> C]CHO	Choline biochemistry	Shao et al. 2014	Tolvanen et al. 2010	Piert et al. 2009
[ <sup>11</sup> C]DASB	[ <sup>11</sup> C]DASB	Serotonin transporter	Shao et al. 2014	Lu et al. 2004	Albin et al. 2008
[ <sup>11</sup> C]Dihydrotrabenzazine	[ <sup>11</sup> C]DTBZ	Vesicular monoamine transporter 2 (VMAT2)	Shao et al. 2014	Murthy et al. 2008	Koeppel et al. 1995
[ <sup>11</sup> C]Epinephrine	[ <sup>11</sup> C]EPI	Norepinephrine Transporter (NET)	Chakraborty et al. 1993	Wrobel et al. 1997	Münch et al. 2000
[ <sup>11</sup> C]Flumazenil	[ <sup>11</sup> C]FMZ	GABA <sub>A</sub> Receptors	Shao et al. 2011a	Laymon et al. 2012	Koeppel et al. 1991
[ <sup>11</sup> C]meta-Hydroxyephedrine	[ <sup>11</sup> C]HED	NET, Sympathetic nervous system	Shao et al. 2014	Wrobel et al. 1997 and Supporting Information	Duvernoy et al. 2016
[ <sup>11</sup> C]LY2795050	[ <sup>11</sup> C]LY2795050	Kappa opioid receptors	Yang et al. 2018	See Supporting Information	<sup>b</sup> ; Naganawa et al. 2015
[ <sup>11</sup> C]Methionine	[ <sup>11</sup> C]MET	Amino acid	Shao et al. 2014	DeLoar et al. 1998	Miller et al. 2019
[ <sup>11</sup> C]Methoxytrabenzazine	[ <sup>11</sup> C]MTBZ	VMAT2	DaSilva et al. 1993a	Wrobel et al. 1997	Vander Borght et al. 1995
[ <sup>11</sup> C]Methylphenidate	[ <sup>11</sup> C]MPH	Dopamine transporter	Moran et al. 2010	See Supporting Information	Albin et al. 2009
[ <sup>11</sup> C]N-Methylpiperidyl benzilate	[ <sup>11</sup> C]NMBP	mAChR	Mulholland et al. 1995	Mulholland et al. 1995	Zubieta et al. 2001
[ <sup>11</sup> C]OMAR/[ <sup>11</sup> C]JHU 75528	[ <sup>11</sup> C]OMAR	Cannabinoid 2 receptors	Shao et al. 2015	Wong et al. 2010	Wong et al. 2010
[ <sup>11</sup> C]Palmitate	[ <sup>11</sup> C]PALM	Fatty acid metabolism	Runkle et al. 2011	Christensen et al. 2017	<sup>b</sup> ; de Jong et al. 2009
[ <sup>11</sup> C]PBR28	[ <sup>11</sup> C]PBR28	Translocator protein 18 kDa (TSPO)	Shao et al. 2014	Brown et al. 2007	<sup>b</sup> Kreisi et al. 2016
[ <sup>11</sup> C]Pittsburgh Compound B	[ <sup>11</sup> C]PIB	Amyloid plaques	Shao et al. 2014	O'Keefe et al. 2009	Burke et al. 2011
[ <sup>11</sup> C]((E)-N-(3-iodoprop-2-enyl)-2β-(4'-tolyl) nortropane)	[ <sup>11</sup> C]PEZI	Dopamine transporter	Dollé et al. 2000; Halldin et al. 2003	Ribeiro et al. 2007	<sup>b</sup> ; Halldin et al. 2003

**Table 1** Radiotracers used clinically at the University of Michigan (Continued)

Radiotracer	Abbreviation	Application	Radioynthesis	Dosimetry	Historical Imaging
[ <sup>11</sup> C]Phenylephrine	[ <sup>11</sup> C]PHEN	NET	Del Rosario et al. 1996	Wrobel et al. 1997	Raffel et al. 1996
(R)-N-Methyl- <sup>11</sup> C PK11195	[ <sup>11</sup> C]PK11195	TSPO	Alves et al., 2013	Hirvonen et al. 2010	Junck et al. 1989
[ <sup>11</sup> C]PMP	[ <sup>11</sup> C]PMP	Acetylcholinesterase	Shao et al. 2014	See Supporting Information	Kuhl et al. 1999
[ <sup>11</sup> C]Raclopride	[ <sup>11</sup> C]RAC	Dopamine D <sub>2</sub> receptors	Shao et al. 2014	Ribeiro et al. 2005	Scott et al. 2006
[ <sup>11</sup> C]Ro-54,864	[ <sup>11</sup> C]Ro-54,864	TSPO	Watkins et al. 1988	see Supporting Information <sup>a</sup>	Junck et al. 1989
[ <sup>11</sup> C]Sarcosine	[ <sup>11</sup> C]SARC	Sarcosine biochemistry	Piert et al. 2017	Piert et al. 2017	Piert et al. 2017
[ <sup>11</sup> C]Scopolamine	[ <sup>11</sup> C]SCOP	mAChR	Mulholland et al. 1988	Frey et al. 1992	Frey et al. 1992
[ <sup>11</sup> C]Tetraabenazine	[ <sup>11</sup> C]TBZ	VMAT2	DaSilva et al. 1993b	DaSilva et al. 1994	Kilbourn et al. 1993
[ <sup>11</sup> C]Tropanylbenzilate	[ <sup>11</sup> C]TRB	mAChR	Mulholland et al. 1992	Mulholland et al. 1992	Koepppe et al. 1994
[ <sup>11</sup> C]WAY-100365	[ <sup>11</sup> C]WAY	5-HT <sub>1A</sub> Receptor	Krasikova et al. 2009	Parsey et al. 2005	Mickey et al. 2008
<b>[<sup>18</sup>F]Radiotracers</b>					
[ <sup>18</sup> F]Flortaucipir	[ <sup>18</sup> F]JAV1451; [ <sup>18</sup> F]T807; Tauvid	Tau	∑; Mossine et al. 2017	Choi et al. 2016	Drake et al. 2019; Kramer et al. 2020
3-(1,4-Diazabicyclo[3.2.2] nonan-4-yl)-6-[ <sup>18</sup> F]fluoro-diben-zolb.d]thiophene 5,5-dioxide	[ <sup>18</sup> F]JHU82132, [ <sup>18</sup> F]ASEM	α7 nicotinic acetylcholine receptor (nAChR)	Gao et al. 2013 and Supporting Information	Wong et al. 2014 and Supporting Information	b; Wong et al. 2014
Fluciclovine (anti-1-Amino-3- <sup>18</sup> F-fluorocyclobutane-1-carboxylic acid)	[ <sup>18</sup> F]FACBC; Auxumin	Amino acid transport	∑; Sörensen et al. 2013	Nye et al. 2007; McParland et al. 2010	b; Songmen et al. 2019
[ <sup>18</sup> F]Fluoroazomycin arabinoside	[ <sup>18</sup> F]FAZA	Tumor hypoxia	Shao et al. 2011b	Savi et al. 2017	Beck et al., 2007
2-[ <sup>18</sup> F]Fluoro-2-deoxy-D-glucose	[ <sup>18</sup> F]FDG	Glucose metabolism	Richards and Scott 2012; Sowa et al. 2018	Srinivasan et al. 2020	Koepppe et al. 2005
[ <sup>18</sup> F]6-Fluoro-L-DOPA	[ <sup>18</sup> F]FDOPA	Dopamine	See Supporting Information, Mossine et al. 2019, 2020	Kaushik et al. 2013; Mejia et al. 1991	Minn et al. 2009
[ <sup>18</sup> F]-Fluoroethoxy- benzovesamicol	[ <sup>18</sup> F]FEOBV	Vesicular acetylcholine transporter	Shao et al. 2011b	Petrou et al. 2014	Petrou et al. 2014
[ <sup>18</sup> F]Fluorocholeline	[ <sup>18</sup> F]FCH	Choline biochemistry	Rodnick et al. 2013	DeGrado et al. 2002; Fabbri et al. 2014	Davenport et al. 2020
[ <sup>18</sup> F]Florbetapir	Amyvid; [ <sup>18</sup> F]JAV45	Amyloid plaques	c	Joshi et al. 2014	Frey and Koepppe 2016

**Table 1** Radiotracers used clinically at the University of Michigan (Continued)

Radiotracer	Abbreviation	Application	Radioynthesis	Dosimetry	Historical Imaging
[ <sup>18</sup> F]Fluoro-3'-deoxy-3'-L-fluorothymidine	[ <sup>18</sup> F]FLT	Cellular proliferation	Shao et al. 2011b	Vesselle et al. 2003; Mendes et al. 2018	Bertagna et al. 2013
[ <sup>18</sup> F]Flubatine	[ <sup>18</sup> F]FLBT	α <sub>4</sub> β <sub>2</sub> nAChR	Hockley et al. 2013	Kranz et al. 2016	Sattler et al. 2012
[ <sup>18</sup> F]Flutemetamol	Vizamy!, [ <sup>18</sup> F]GE67	Amyloid plaques	Snellman et al. 2014	Koole et al. 2009	Frey and Koeppe 2016
[ <sup>18</sup> F]Fluoromisonidazole	[ <sup>18</sup> F]FMISO	Tumor hypoxia	Riss et al. 2012	Graham et al. 1997	Bruehlmeier et al. 2004
[ <sup>18</sup> F]Fluoropropyl-dihydrotetraabenazine	[ <sup>18</sup> F]FP-TBZ, [ <sup>18</sup> F]AV133	VMAT2	Lin et al. 2010	Lin et al. 2010	Kilbourn and Koeppe 2019
[ <sup>18</sup> F]GBR13119 / [ <sup>18</sup> F]GBR12909	[ <sup>18</sup> F]GBR	DAT	Haka and Kilbourn 1988, 1990	Kilbourn et al. 1989	Koeppe et al. 1990b
4-[ <sup>18</sup> F]Fluoro- <i>m</i> -hydroxyphenethylguanidine	[ <sup>18</sup> F]MHPG	NET	Raffel et al. 2018	Raffel et al. 2018	Raffel et al. 2018
2'-Methoxyphenyl-( <i>N</i> -2'-pyridinyl)- <i>p</i> - <sup>18</sup> F-fluoro-benzamidoethylpiperazine	[ <sup>18</sup> F]MPPF	5-HT <sub>1A</sub> Receptor	Shao et al. 2011b	See Supporting Information	b; Aznavour and Zimmer 2007
[ <sup>18</sup> F]Sodium Fluoride	[ <sup>18</sup> F]NaF	Bone imaging	Shao et al. 2011b	Segall et al. 2010; Silveira et al. 2010	Wong and Piert 2013
[ <sup>18</sup> F]N-Methyl Lansoprazole	[ <sup>18</sup> F]NML	Tau	Kramer et al. 2020	Kramer et al. 2020	Kramer et al. 2020
4-[ <sup>18</sup> F]Fluoro- <i>p</i> -hydroxyphenethylguanidine	[ <sup>18</sup> F]PHPG	NET	Raffel et al. 2018	Raffel et al. 2018	Raffel et al. 2018
<b>Other Radiotracers</b>					
[ <sup>13</sup> N]Ammonia	[ <sup>13</sup> N]NH <sub>3</sub>	Blood flow	Scott 2012	Yi et al. 2015	Beanlands et al. 1994
[ <sup>15</sup> O]Water	[ <sup>15</sup> O]H <sub>2</sub> O	Blood flow	Dick and Watkins 2015	Brihaye et al. 1995	Minoshima et al. 1993
[ <sup>68</sup> Ga]DOTATATE	NETSPOT	Somatostatin receptors	NETSPOT prescribing information 2016	Walker et al. 2013	b; Fallahi et al. 2019
[ <sup>68</sup> Ga]PSMA-HBEDCC	[ <sup>68</sup> Ga]PSMA-11	Prostate specific membrane antigen	See Supporting Information; Rodnick et al. 2020	Afshar-Oromieh et al. 2016; Sandgren et al. 2019	Rodnick et al. 2020

<sup>a</sup>Historical dosimetry data is no longer extant. Biodistribution data are provided to enable estimation of dosimetry; <sup>b</sup>UM imaging data not yet published; <sup>c</sup>Commercially available under an approved (A)NDA; <sup>d</sup>Commercially available under an IND

according to current Good Manufacturing Practice (cGMP) using the guidelines outlined in the US Pharmacopeia, (USP < 823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses 2020).

### Dosimetry

Radiation-absorbed-dose estimates can either be obtained from literature sources or determined using the OLINDA/EXM 1.0 software package (Stabin et al. 2005). Table 1 provides literature sources of dosimetry wherever available. For any radiotracers where literature dosimetry is unavailable, dosimetry is provided in the [Supporting Information](#).

### Imaging

Research PET scans have been conducted since the first PET scanner was installed at the University of Michigan (UM) in the 1980s. Historical examples of imaging studies mostly conducted at our Center with the various radiotracers are provided in Table 1, including practical information on both scanning protocols and image kinetic analysis. Injected dose (MBq), mass dose limits ( $\mu\text{g}$ ) and historical numbers of subjects scanned are provided in Table 2.

### Discussion

At the University of Michigan we have a long history of using PET radiotracers in clinical research studies (using both the RDRC and IND mechanisms). Detailed information for 55 such radiotracers is provided in Table 1, including references for radiosyntheses and dosimetry available in the peer-reviewed literature. Synthesis ( $[^{11}\text{C}]$ butanol,  $[^{18}\text{F}]$ ASEM,  $[^{18}\text{F}]$ FDOPA,  $[^{68}\text{Ga}]$ PSMA-11) and dosimetry ( $[^{18}\text{F}]$ ASEM,  $[^{11}\text{C}]$ butanol,  $[^{11}\text{C}]$ HED,  $[^{11}\text{C}]$ LY2795050,  $[^{11}\text{C}]$ MPH,  $[^{18}\text{F}]$ MPPE,  $[^{11}\text{C}]$ PMP,  $[^{11}\text{C}]$ RO-54864) information that has not previously been published is provided in the [Supporting Information](#) associated with this article. Pharmacological dose and radioactivity dosing information for the PET drugs is also provided (Table 2), along with historical numbers of administrations to subjects at the University of Michigan PET Center. Rationale for those radiotracers without mass dose limits is provided in the [Supporting Information](#).

As noted above, a study conducted under RDRC oversight cannot exceed 30 subjects without special provisions. The PET drugs corresponding to some of the larger numbers of subjects discussed herein have been used in numerous different RDRC studies over the course of many years (and decades in some instances). In the event any given study exceeded 30 research subjects, the RDRC committee filed a special summary (Form FDA 2915). At the doses specified, no pharmacological or physiological changes were observed after intravenous administration of any of the PET drugs, and the basic science studies were conducted without exceeding any regulatory radiation dose limits. All scans have been reported to the US FDA in the annual RDRC reports required by the agency.

### Conclusion

While an IND (or eIND) is the dominant route to FDA approval for first-in-man studies, collection of the requisite data and preparation of the application can be a daunting



**Table 2** Dosing information

Radiotracer	Injected Dose (MBq)	Mass dose limit	Number of subjects scanned	Clinically detectable pharmacological effects in humans
<b>[<sup>11</sup>C]Radiotracers</b>				
[ <sup>11</sup> C]ACE	740	None	475	No
[ <sup>11</sup> C]ACHC	740	≤5000 µg/subject	2	No
[ <sup>11</sup> C]BMP	444	≤4625 µg/subject	65	No
[ <sup>11</sup> C]BUT	555	≤125 µg/kg	0 <sup>a</sup>	a
[ <sup>11</sup> C]CFN	555	≤0.03 µg/kg	1492	No
[ <sup>11</sup> C]CHO	592	None	44	No
[ <sup>11</sup> C]DASB	666	≤8 µg/subject	179	No
[ <sup>11</sup> C]DTBZ	555	≤50 µg/subject	1823	No
[ <sup>11</sup> C]EPI	740	< 9 µg/subject epinephrine & ≤1 µg/subject norepinephrine precursor	96	No
[ <sup>11</sup> C]FMZ	370	≤50 µg/subject	668	No
[ <sup>11</sup> C]HED	666	≤50 µg/subject <sup>b</sup>	643	No
[ <sup>11</sup> C]LY2795050	555	≤10 µg/subject	0 <sup>c</sup>	c
[ <sup>11</sup> C]MET	444	None	129	No
[ <sup>11</sup> C]MTBZ	580	≤10 µg/subject	6	No
[ <sup>11</sup> C]MPH	666	≤25 µg/subject	170	No
[ <sup>11</sup> C]NMBP	740–1480	≤127 µg/subject <sup>d</sup>	59	No
[ <sup>11</sup> C]OMAR	666	0.14 µg/kg	0 <sup>e</sup>	e
[ <sup>11</sup> C]PALM	740	None	8	No
[ <sup>11</sup> C]PBR28	666	≤10 µg/subject	34	No
[ <sup>11</sup> C]PiB	666	≤13 µg/subject	592	No
[ <sup>11</sup> C]PE2I	555	≤6.3 µg/subject	1	No
[ <sup>11</sup> C]PHEN	740	≤6800 µg/subject	29	No
[ <sup>11</sup> C]PK11195	888	≤420 µg/subject	118	No
[ <sup>11</sup> C]PMP	555	≤200 µg/subject	801	No
[ <sup>11</sup> C]RAC	555	≤50 µg/subject	627	No
[ <sup>11</sup> C]Ro-54,864	555	≤160 µg/subject	6	No
[ <sup>11</sup> C]SARC	592	None	20	No
[ <sup>11</sup> C]SCOP	1480	≤50 µg/subject	14	No
[ <sup>11</sup> C]TBZ	1018	≤10 µg/subject	2	No
[ <sup>11</sup> C]TRB	1110	≤31 µg/subject	26	No
[ <sup>11</sup> C]WAY-100365	555	≤15 µg/subject	51	No
<b>[<sup>18</sup>F]Radiotracers</b>				
[ <sup>18</sup> F]AV1451	370	≤20 µg/subject	92	No
[ <sup>18</sup> F]ASEM	370	≤0.67 µg/subject	1	No
Auxumin	370	≤20 µg/subject	228 <sup>f</sup>	No
[ <sup>18</sup> F]FAZA	296	≤3.5 µg/subject	14	No
[ <sup>18</sup> F]FDG	185–296	None	6804	No
[ <sup>18</sup> F]FDOPA	148	≤15 µg/subject	0 <sup>g</sup>	g
[ <sup>18</sup> F]FEOBV	296	≤1.23 µg/subject	308	No
[ <sup>18</sup> F]FCH	222	≤100 µg/subject	67	No
Amyvid	370	≤50 µg/subject	222	No

**Table 2** Dosing information (Continued)

Radiotracer	Injected Dose (MBq)	Mass dose limit	Number of subjects scanned	Clinically detectable pharmacological effects in humans
[ <sup>18</sup> F]FLT	370	≤20 µg/subject	8	No
[ <sup>18</sup> F]FLBT	296	≤0.02 µg/kg	92	No
Vizamyl	370	≤20 µg/subject	11	No
[ <sup>18</sup> F]FMISO	370	≤15 µg/subject	8	No
[ <sup>18</sup> F]FP-TBZ	370	≤7.5 µg/subject	23	No
[ <sup>18</sup> F]GBR	148	≤900 µg/subject	2	No
[ <sup>18</sup> F]MHPG	241	≤10 µg/subject	17	No
[ <sup>18</sup> F]MPPF	259	≤2 µg/subject	34	No
[ <sup>18</sup> F]NaF	222	None	9	No
[ <sup>18</sup> F]NML	370	≤10 µg/subject	6	No
[ <sup>18</sup> F]PHPG	241	≤10 µg/subject	15	No
<b>Other Radiotracers</b>				
[ <sup>13</sup> N]NH <sub>3</sub>	740	None	1472	No
[ <sup>15</sup> O]Water	555	None	1153	No
NETSPOT	200	≤40 µg/subject	981 <sup>f</sup>	No
[ <sup>68</sup> Ga]PSMA-11	185	≤10 µg/subject	751 <sup>f</sup>	No

<sup>a</sup>[<sup>11</sup>C]Butanol is validated for clinical production but studies have not yet commenced. We do not expect clinically detectable pharmacological effects as the mass limit (≤125 µg/kg) was selected since it is 1000 times below the NOEL (125 mg/kg, see: Wagner 2005); <sup>b</sup> combined mass of HED and metaraminol precursor must be ≤50 µg/subject; <sup>c</sup> [<sup>11</sup>C]LY2795050 is validated for clinical production but studies have not yet commenced at UM. We do not expect clinically detectable pharmacological effects as the mass limit (≤10 µg/subject) has been used without significant adverse events at other institutions (see: Naganawa et al. 2015); <sup>d</sup> See published limits (Yoshida et al. 1998); <sup>e</sup> [<sup>11</sup>C]OMAR is validated for clinical production but studies have not yet commenced at UM. We do not expect clinically detectable pharmacological effects as the mass limit (≤0.14 µg/kg) has been used without significant adverse events at other institutions (see: Wong et al. 2010); <sup>f</sup> Includes subjects numbers scanned for clinical care and research; <sup>g</sup> [<sup>18</sup>F]FDOPA is validated for clinical production but studies have not yet commenced. We do not expect clinically detectable pharmacological effects as the mass limit (≤15 µg/subject) is significantly less than administered masses historically used when employing the electrophilic synthesis of [<sup>18</sup>F]FDOPA (13 mg/62 kg subject, see: Chevalme et al. 2007)

and resource intensive task. Proceeding under approval of a Radioactive Drug Research Committee therefore represents an attractive mechanism for clinical studies of compounds that have (a) already been studied in man and (b) are well characterized in terms of pharmacology and dosimetry. Initiation of a new study for such an established compound is contingent upon access to mass dose and dosimetry data. The data provided herein will streamline future RDRC approval, and facilitate further basic science investigation of 55 PET drugs that target functionally relevant biomarkers in high impact disease states.

### Supplementary Information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s41181-020-00110-z>.

**Additional file 1.**

### Abbreviations

ANDA: Abbreviated new drug application; Bq: Becquerels; cGMP: Current good manufacturing practice; eIND: Exploratory IND; FDA: Food and Drug Administration; IND: Investigational new drug; NDA: New drug application; PET: Positron emission tomography; QC: Quality control; RDRC: Radioactive drug research committee; USP: United States Pharmacopeia

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### Authors' contributions

IMJ and PJHS analyzed data and wrote the manuscript. SJL, ARS, JT, XS, MER, LB, MC, SP and AFB conducted radiosyntheses. VER maintains historical PET records and databases. JR is the lead PET technologist who coordinated scheduling and clinical dosing. BGH, BDH, MC and JT provided quality control and/or quality assurance for PET drug manufacture. LEB coordinated RDRC/IRB submissions. DMR calculated dosimetry. KAF, RAK, MRK and PJHS have supervision responsibility. KAF is Chief of Nuclear Medicine and the authorized user physician. The author(s) read and approved the final manuscript.

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### Availability of data and materials

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### Ethics approval and consent to participate

This article does not contain any original studies with human or animal subjects performed by any of the authors.

### Consent for publication

All authors gave their consent for publication.

### Competing interests

The authors declare no competing financial interests.

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